

Diagnostic work-up of bile duct strictures: European Society of Gastrointestinal Endoscopy (ESGE) Guideline



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MAIN RECOMMENDATIONS

1 ESGE recommends the combination of endoscopic ultrasound-guided tissue acquisition (EUS-TA) and endoscopic retrograde cholangiopancreatography (ERCP)-based tissue acquisition as the preferred diagnostic approach for tissue

acquisition in patients with jaundice and distal extrahepatic biliary stricture in the absence of a pancreatic mass.

2 ESGE suggests that brushing cytology should be completed along with fluoroscopy-guided biopsies, wherever technically feasible, in patients with perihilar biliary strictures.

3 ESGE suggests EUS-TA for perihilar strictures when ERCP-based modalities yield insufficient results, provided that curative resection is not feasible and/or when cross-

sectional imaging has shown accessible extraluminal disease.

4 ESGE suggests using standard ERCP diagnostic modalities at index ERCP. In the case of indeterminate biliary strictures, ESGE suggests cholangioscopy-guided biopsies, in addition to standard ERCP diagnostic modalities. Additional intraductal biliary imaging modalities can be selectively used, based on clinical context, local expertise, and resource availability.

ABBREVIATIONS

AE	adverse events
CA19-9	carbohydrate antigen 19-9
CBD	common bile duct
CCA	cholangiocarcinoma
CEA	carcinoembryonic antigen
CECT	contrast-enhanced computed tomography
CLE	confocal laser endomicroscopy
ERCP	endoscopic retrograde cholangiopancreatography
ERCP-TA	ERCP-based tissue acquisition
EUS	endoscopic ultrasound
EUS-TA	EUS-guided tissue acquisition
FNA	fine-needle aspiration
FNB	fine-needle biopsy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDUS	intraductal ultrasound
IgG4	immunoglobulin G4 level
IgG4-SC	IgG4-related sclerosing cholangitis
PDAC	pancreatic ductal adenocarcinoma
PSC	primary sclerosing cholangitis
QALY	quality-adjusted life year
RCT	randomized controlled trial
SOC	single-operator cholangioscopy

SCOPE AND PURPOSE

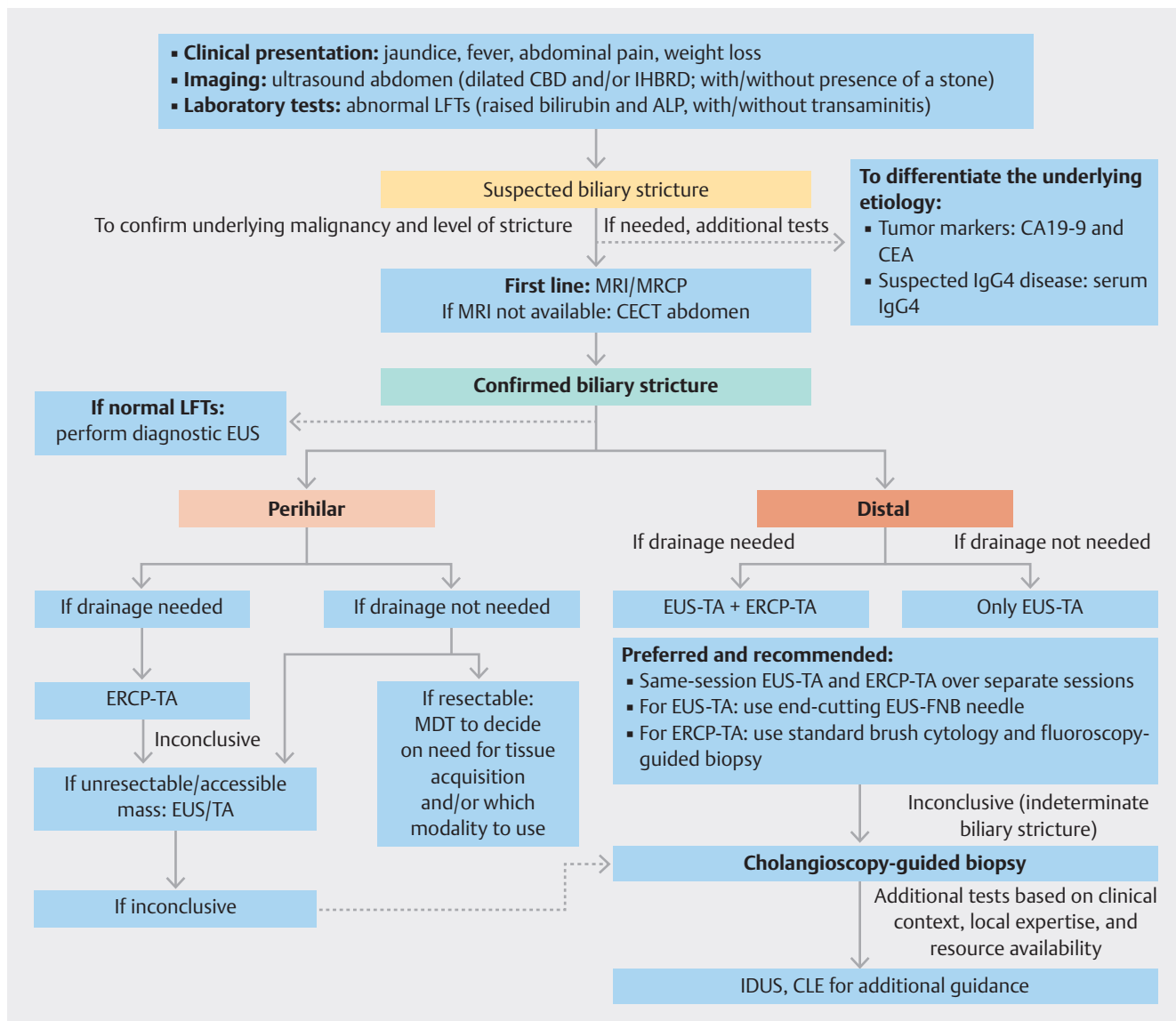
This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). ESGE Guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They are intended to be an educational tool to provide information that may support endoscopists in providing care to patients.

1 Introduction

A biliary stricture or bile duct stricture is defined as a narrowing or blockage of either the intrahepatic and/or extrahepatic biliary system, with concomitant upstream biliary duct dilatation, which impedes the antegrade flow of bile from the liver to the intestine. Symptomatic biliary strictures commonly present with jaundice (with/without cholangitis) and infrequently with liver abscess or secondary biliary cirrhosis. The most common benign etiology is iatrogenic injury, but it is determining the presence or absence of underlying malignancy that presents a diagnostic challenge for any clinician, as it has implications for oncologic and surgical decision-making.

The diagnostic armamentarium includes: laboratory tumor markers; cross-sectional imaging (computed tomography [CT], magnetic resonance imaging [MRI], and/or magnetic resonance cholangiopancreatography [MRCP]); endoscopic retrograde cholangiopancreatography (ERCP), which may include brushings, forceps biopsy, cholangioscopy-guided biopsy, and/or intraductal imaging; and endoscopic ultrasound (EUS), with/without fine-needle biopsy (FNB). The techniques for diagnosis and subsequent drainage (if needed) vary dependent on the anatomic location of the biliary stricture (intrahepatic, hilar, or extrahepatic) (► Fig. 1).

The European Society of Gastrointestinal Endoscopy (ESGE) commissioned this guideline in 2023 to deal specifically with the diagnostic approach to biliary strictures (not associated with an underlying pancreatic or abdominal mass). The goal of this guideline is to provide evidence-based recommendations (based on Grading of Recommendations Assessment, Development and Evaluation [GRADE] criteria), focusing on four separate sections: laboratory tests and cross-sectional imaging; extrahepatic biliary stricture; perihilar stricture; and cholangioscopy with intraductal imaging. The subject of endoscopic tissue sampling of pancreatic masses has already been discussed in a previous ESGE guideline [1], so has not been dealt with here.



► **Fig. 1** Proposed algorithm for the diagnosis of bile duct strictures.

ALP, alkaline phosphatase; CA19-9, carbohydrate antigen 19-9; CBD, common bile duct; CEA, carcinoembryonic antigen; CECT, contrast-enhanced computed tomography; CLE, confocal laser endomicroscopy; ERCP, endoscopic retrograde cholangiopancreatography; ERCP-TA, ERCP-based tissue acquisition; EUS, endoscopic ultrasound; EUS-FNB, EUS-guided fine-needle biopsy; EUS-TA, EUS-guided tissue acquisition; IDUS, intraductal ultrasound; IgG4, immunoglobulin G4 level; IHBRD, intrahepatic biliary radicle dilatation; LFTs, liver function tests; MDT, multidisciplinary team; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

2 Methods

The ESGE Guideline Committee Chair (K.T.) appointed a Leader (A.F.), who invited a list of authors (the panel) to participate in the project development, and four task forces were created to deal with the different aspects of the guideline. An online meeting was held on 22 June 2023, where task force members were allotted to different task forces and decisions were finalized on the subheadings for the Guideline and questions to be formed by each task force, as well as the deadline for the literature search and draft of the manuscript. All task force members were required to disclose potential financial and intellectual

conflicts of interest, which were addressed according to the ESGE policies.

The guideline was developed using the GRADE framework [2] (► **Table 1**). The relevant clinical questions were developed a priori and listed in the PICO format (**Table 1s**, see online-only Supplementary material).

Each task force performed a systematic literature search using PubMed/MEDLINE, Embase, Scopus, and the Cochrane library to identify publications from inception till December 2023 (restricted to papers published in the English language), focusing on meta-analyses and published prospective studies, particularly randomized controlled trials (RCTs), performed in humans (**Table 2s**). Retrospective analyses and pilot studies

► **Table 1** Interpretation of the certainty in evidence of effects and of strong and conditional recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Certainty	Description	
High	We are very confident that the true effect lies close to that of the estimate of the effect	
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect	
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect	
Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not	Most individuals in this situation would want the suggested course of action, but many would not
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision-making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences
For policymakers	The recommendation can be adapted as policy or performance measure in most situations	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate

were also included if they addressed topics not covered in the prospective studies. For the purpose of the current guideline, only studies which pertained to “purely” bile duct strictures have been included when drafting the recommendations.

After further exploration of their content, all the relevant articles were included and summarized in the literature tables for the key topics.

Further details on the methodology of ESGE guideline development have been reported elsewhere [3]. In addition, various web meetings were held between the leader of the guideline (A.F.) and the task-force leaders to discuss and resolve issues, and to finalize the recommendations.

By September 2024, a draft of all of the recommendations in the Guideline was prepared by the listed authors. Following approval by the Leader (A.F.), the draft was reviewed by two members of the ESGE Governing Board and by external reviewers, and was then sent for further comments to the ESGE National Societies and individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final version of the manuscript.

This Guideline was issued in 2024 and will be considered for review if new and relevant evidence becomes available. Any updates to the Guideline in the interim period will be noted on the ESGE website: <https://www.esge.com/esge-guidelines.html>.

3 Results and recommendations

A summary of all recommendations is provided in ► **Table 2**.

The presence of a biliary stricture portends a medical challenge for any endoscopist, in terms of its anatomy and difficulty in making a diagnosis, and subsequently in deciding on its management [4]. Differentiating whether a biliary stricture is either

benign or malignant is of the foremost importance as it has implications in surgical and oncologic decision-making, hence the need to make a safe, accurate, and expedient diagnosis [5]. The gold standard has always been tissue diagnosis, wherein lies the role of endoscopy (ERCP or EUS) in providing cytologic or histologic specimens. Among the most common benign causes of biliary stricture is iatrogenic bile duct injury, whereas among malignant causes, pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) are the commonest causes of distal and proximal stricture, respectively [6]. A list of the main etiologies of biliary stricture is shown in the list next page. Sometimes biliary strictures can present without an underlying mass, which occasionally makes them unidentifiable on cross-sectional imaging, as well as limiting the utility of tissue diagnosis in view of the desmoplastic nature of the tumors [7,8,9].

3.1 Laboratory tests and cross-sectional imaging

RECOMMENDATION 1

ESGE suggests against the use of tumor markers alone to discriminate between malignant and benign causes of a stricture in patients with suspected biliary stricture presenting with jaundice; ESGE suggests the use of laboratory tests in addition to other investigations (imaging and histopathology) in making a definite diagnosis. Conditional recommendation, very low quality of evidence.

Inexpensive and readily available serologic tests that can rapidly differentiate between benign and malignant causes of biliary stricture would allow prioritization of patients.

► **Table 2** ESGE recommendations on the diagnostic work-up of biliary strictures.

Recommendations	Strength of recommendation	Quality of evidence
1 ESGE suggests against the use of tumor markers alone to discriminate between malignant and benign causes of a stricture in patients with suspected biliary stricture presenting with jaundice; ESGE suggests the use of laboratory tests in addition to other investigations (imaging and histopathology) in making a definite diagnosis	Conditional	Very low
2 ESGE suggests the use of MRI/MRCP over CECT to discriminate between malignant and benign cause of obstruction and to detect the level of the stricture in patients with suspected biliary stricture presenting with jaundice and/or biochemical evidence of cholestasis	Conditional	Low
3 ESGE recommends the combination of EUS-TA and ERCP-TA as the preferred diagnostic approach for tissue acquisition in patients with jaundice and distal extrahepatic biliary stricture in the absence of a pancreatic mass	Strong	Moderate
4 ESGE suggests performing EUS and ERCP in the same session as this approach does not increase the risk of adverse events nor impair the effectiveness of the techniques	Conditional	Very Low
5 ESGE suggests performing EUS in patients with suspected biliary stricture and/or unexplained common bile duct dilatation even in the absence of abnormal laboratory tests	Conditional	Very Low
6 ESGE suggests that brushing cytology should be completed along with fluoroscopy-guided biopsies, wherever technically feasible, in patients with perihilar biliary strictures	Conditional	Low
7 ESGE suggests EUS-TA for perihilar strictures when ERCP-based modalities yield insufficient results, provided that curative resection is not feasible and/or when cross-sectional imaging has shown accessible extraluminal disease	Conditional	Low
8 ESGE suggests using standard ERCP diagnostic modalities at index ERCP. In the case of indeterminate biliary strictures, ESGE suggests taking cholangioscopy-guided biopsies, in addition to standard ERCP diagnostic modalities. Additional intraductal biliary imaging modalities can be selectively used, based on clinical context, local expertise, and resource availability	Conditional	Very Low

CECT, contrast-enhanced computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ERCP-TA, ERCP-based tissue acquisition; EUS, endoscopic ultrasound; EUS-TA, EUS-guided tissue acquisition; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

MAIN ETIOLOGIES OF BILIARY STRICTURES

Malignant

- Pancreatic cancer
- Cholangiocarcinoma
- Gallbladder cancer
- Hepatocellular carcinoma
- Ampullary cancer
- Lymphoma
- Rare neoplasia (cystadenocarcinoma, mixed hepatocellular-cholangiocellular cancer)
- Metastasis (colon cancer, breast cancer, renal cell cancer)

Fibroinflammatory

- Chronic pancreatitis
- Primary sclerosing cholangitis
- Autoimmune pancreatitis
- IgG4-mediated cholangitis
- Sarcoidosis
- Recurrent pyogenic cholangitis
- Extrinsic compression by pancreatic fluid collections

Iatrogenic

- Cholecystectomy
- Liver transplantation
- Local cancer treatment

Vascular

- Portal hypertensive biliopathy
- Ischemic biliary injury

Other

- AIDS cholangiopathy
- Mirizzi syndrome

AIDS, acquired immunodeficiency syndrome; IgG4, immunoglobulin G4.

The two most commonly studied tumor markers related to the pancreaticobiliary system are the carbohydrate antigen 19–9 (CA19–9) and carcinoembryonic antigen (CEA). Both are glycoprotein tumor markers with the immune-determinant epitope on the carbohydrate and protein moiety of the molecule, respectively [10, 11].

3.1.1 Benefits

The usefulness of these tumor markers has been shown in multiple studies, regarding their role in staging, evaluation of resectability status, and assessment of prognosis and of recurrence on follow-up [12, 13, 14, 15, 16].

The panel conducted a comprehensive meta-analysis to determine the accuracy of CA19–9 and CEA levels in differentiating benign versus malignant etiologies. After a comprehensive literature search, 11 studies for CA19–9 [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27] and four studies for CEA levels [26, 28, 29, 30] were selected for analysis (inclusion criteria: CA19–9 >37 U/mL and CEA >2.5–5 ng/mL, with studies reporting the accuracy of malignant vs. benign cases) (**Table 3s**). The pooled accuracy of CA19–9 levels for discrimination between benign and malignant causes of biliary stricture was 81% (95%CI 76%–87%; $I^2 = 84.7\%$) (**Fig. 1s, part a**), whereas the pooled accuracy of CEA levels was 70% (95%CI 62%–78%; $I^2 = 63.7\%$) (**Fig. 1s, part b**). For malignant cases, the sensitivity of CA19–9 levels was 68%–85%, with a specificity of 64%–87%. Similarly, for CEA levels, the sensitivity and specificity were 25%–82% and 83%–92%, respectively.

Morris-Stiff et al. have also reported that the combination of tumor markers (CA19–9) with cross-sectional imaging increases the sensitivity and specificity from 85% to 97% and 70% to 89%, respectively [21]. Similarly, the decline in CA19–9 post-biliary drainage is slower, and the average reduction is smaller in malignant cases (50%) compared with benign cases (100%) [17]. All these factors highlight that the role of tumor markers (especially CA19–9 and CEA) is complementary to other investigations, like cross-sectional imaging and tissue diagnosis, for determining the underlying etiology of biliary strictures.

Additionally, when IgG4-related sclerosing cholangitis (IgG4-SC) is clinically suspected, especially in a setting of distal common bile duct (CBD) stricture and autoimmune pancreatitis, serologic testing in the form of serum IgG4 levels is usually the first-line investigation, having been reported to be elevated in 90% of IgG4-SC cases [31, 32].

3.1.2 Harms

Numerous studies have reported elevated CA19–9 levels (>37 U/mL) in various pancreaticobiliary cancers (especially PDAC, CCA, and gallbladder cancer). CA19–9 proved a more useful marker in the absence of cholestasis or cholangitis (sensitivity 78% vs. 74%; specificity 83% vs. 42%) [33]. Increasing the cutoff value decreases the sensitivity and precludes its clinical utility. CA19–9 has also been shown to be elevated in a number of benign conditions, such as liver diseases (primary sclerosing cholangitis [PSC] and cirrhosis, among others), obstructive jaundice, pancreatitis, and even in renal, respiratory, and rheumatologic cases [34]. Moreover, CA19–9 antigen is an oligosac-

charide corresponding to sialylated Lewis blood group Le^a , whose concentration in serum may be influenced by the patient's secretor status and Lewis genotype [35] (7% of the world's population are nonsecretors). As a result, such false-positive cases are to be interpreted with caution.

As evident in the meta-analysis above, both tumor markers have low pooled accuracy in identifying malignancy as a cause of biliary obstruction. Moreover, high false-positive rates of CA19–9 and CEA have been reported (15% and 18%, respectively) [19]. Higher cutoff values for CA19–9 were suggested in a few studies (e.g. 90 U/mL and 70.5 U/mL), which further decreased the sensitivity [17, 21].

Although the serum IgG4 level is a piece of the diagnostic evidence when IgG4-SC is suspected, its specificity is suboptimal to be used in isolation, without other criteria. Kamisawa et al. reported using a cutoff of >135 mg/dL along with both imaging and histopathologic evidence to formulate a definitive diagnosis [36]. Its sensitivity and specificity are 64%–90% and 87%–93%, respectively [31, 36, 37].

Elevated levels of serum IgG4 have also been reported in patients with CCA (8%–14% of patients), PSC (9%–22%), and pancreatic cancer (6%) [31, 37, 38, 39]. Therefore, owing to the low discrimination value of serum IgG4 levels when used alone and frequent false positives in various diseases, especially PSC and CCA (which may mimic IgG4-SC), IgG4 levels should not be used alone for the diagnosis of IgG4-SC, but only in combination with imaging and histopathology.

In conclusion, laboratory tests and serum tumor markers alone have an unacceptably low accuracy in differentiating between benign and malignant biliary obstruction, especially in the presence of jaundice or cholangitis.

3.1.3 Cost-effectiveness profile

Although measurement of tumor markers is relatively inexpensive, the costs associated with searching for malignancy on the basis of an isolated finding of an elevated tumor marker can amount to thousands of dollars, for example US\$34685 for ERCP and \$37458 for EUS according to a recent cost-effectiveness analysis [40]. Therefore, although specific cost-effectiveness analyses on the use of tumor markers in biliary strictures are lacking, the unacceptably low accuracy of tumor markers alone in detecting neoplasia would determine an increase in the costs of missed diagnoses and an overuse of cross-sectional imaging and endoscopy in false-positive cases.

3.1.4 Environmental impact

Laboratory buildings, processes, and equipment, including single-use plastics, automation, and technologies using vast amounts of energy and water, along with transportation and storage of samples, all add to the environmental burden. Among the suggestions to reduce the carbon footprint in this setting are recycling bins in all laboratory and nonlaboratory areas, reviewing freezer contents regularly and discarding items not needed, performing audits to reduce printing, storing work logs digitally to reduce printing, nonlaboratory staff working from home on a rota basis, using timers or labelling to switch off nonessential equipment when not in use, and using

electronic signatures. Furthermore, reducing sample transport and finding more efficient means of transport represent another challenge to improve this aspect [41].

3.1.5 Certainty of the evidence assessment

The risk of bias assessment for each study can be found in **Table 4s**. Overall, all the included studies were considered to be of good quality. The certainty of evidence in this PICO question was downgraded owing to the fact that there were only non-comparative observational studies included (**Table 5s**). For the main outcome of diagnostic accuracy, further downgrading was applied owing to inconsistency (high heterogeneity), which downgraded the quality of evidence to very low.

RECOMMENDATION2

ESGE suggests the use of MRI/MRCP over contrast-enhanced computed tomography (CECT) to discriminate between malignant and benign causes of obstruction and to detect the level of the stricture in patients with suspected biliary stricture presenting with jaundice and/or biochemical evidence of cholestasis.

Conditional recommendation, low quality of evidence.

The expanding spectrum of therapeutic interventions for the management of biliary stricture mandates that a precise assessment be made beforehand regarding the etiology, location, level, and extent of the disease. This diagnostic algorithm usually follows a two-pronged approach: initial clinical and laboratory examination, followed by cross-sectional imaging. Any imaging procedure that is undertaken should answer two important questions: etiology (benign vs. malignant) and the level of the stricture. The role of imaging in the evaluation of any case of biliary stricture entails confirming the diagnosis (benign vs. malignant), locating the level of stricture (distal, mid, or hilar), staging the disease, assessing the resectability status, and giving preoperative information to the surgeon by providing a proper roadmap and the relevant anatomic and vascular anatomy.

Transabdominal ultrasound has low accuracy in determining the etiology and extent of the disease, with a sensitivity and specificity for biliary obstruction of 31%–100% and 71%–97%, respectively [42,43,44]. In contrast, ERCP (the gold standard) remains the cornerstone in the management of biliary strictures, offering simultaneous tissue diagnosis, but is burdened with complications (4%–10%), such as post-ERCP pancreatitis, bleeding, infection, and perforation, meaning its role for diagnostic purposes has become outdated [42,43,45].

3.1.6 Benefits

MRCP is noninvasive, and does not require contrast injection and ionizing radiation exposure, with minimal risk of post-procedure complications. It provides a panoramic view of the biliary tree (multiplanar capability), both above and below the stricture, which enables diagnosis of the site, nature, and

dimensions of the obstruction, providing a complete overview of the biliary tree to the endoscopist/surgeon. When combined with MRI, it allows indirect visualization of drainage catheters and preoperative evaluation of the extent of disease (staging), which is especially useful in those with altered anatomy. Meanwhile, a contrast-enhanced computed tomography (CECT) scan is quick, with few motion artifacts, and with good patient compliance; however, it involves exposure to radiation and intravenous contrast agents. All these factors give MRI/MRCP a “theoretical edge” over CECT scanning for the evaluation of any cases of biliary stricture [6,46].

For the evaluation of obstructive jaundice, the published literature reports a sensitivity, specificity, and accuracy of MRCP of 81%–100%, 84%–100%, and 90%–96%, respectively [47]. Likewise, a CECT abdomen is highly sensitive (74%–96%) and specific (90%–94%) for the detection of biliary obstruction [42,43,44]. Both modalities can also detect vascular encasement and metastatic disease.

The panel conducted a comprehensive meta-analysis to assess the pooled accuracy of CECT versus MRI/MRCP in determining the level of biliary stricture and malignancy as the etiology. Only head-to-head comparative studies were taken into consideration. For determination of the level of stricture, six studies were analyzed [48,49,50,51,52,53] (**Table 6s**), wherein the pooled accuracy of MRI/MRCP was superior to that of CECT (odds ratio [OR] 3.3, 95%CI 1.2–9.1; $I^2=0\%$) (**Fig. 2s, part a**).

Similarly, 10 studies [47,49,50,51,53,54,55,56,57,58] were analyzed for the pooled accuracy of diagnosing malignant biliary strictures (**Table 7s**), wherein MRI/MRCP again proved superior to CECT (96% vs. 89%; OR 2.1, 95%CI 1.2–3.6; $I^2=12\%$) (**Fig. 2s, part b**). Furthermore, MRI/MRCP has also been shown to avoid the need for unnecessary ERCP in approximately one-third of cases [59], is valuable in the setting of failed ERCP, and offers incremental benefit over ultrasound in pregnant patients with suspected biliary obstruction. MRI/MRCP is also useful in planning for therapeutic ERCP in difficult situations, such as complex hilar strictures, or where additional pancreatic therapy is being contemplated [60,61].

In conclusion, based on the evidence above, ESGE suggests that, in a suspected case of biliary stricture with/without jaundice, MRI/MRCP should be preferred over CECT for the evaluation of both the level and the underlying pathology of the biliary stricture.

3.1.7 Harms

Even though MRCP is superior to CECT in evaluating the cause and level of a biliary stricture, both have their own sets of limitations. Both are operator-dependent modalities, and their diagnostic accuracy varies with the available expertise [62].

Contraindications for the use of MRI/MRCP include the presence of underlying pacemakers, cerebral aneurysm clips (although MRI-compatible devices are now available), and claustrophobia. Furthermore, technical considerations, such as breath-holding, lack of therapeutic ability, and motion artifacts, limit its usefulness in certain situations. The latter leads to poor sensitivity of MRCP for the detection of small stones

(<3–5 mm; 64%), as reported by Guibaud et al. [63]. Motion artifacts are prevalent in the distal portion of the CBD, where small stones usually migrate, thereby decreasing resolution, which has been shown to translate into lower performance for MRCP when evaluating distal over proximal strictures [64]. By extrapolation of these findings, ampullary pathologies may be erroneously diagnosed because of poor performance of MRCP at/near the duodenal wall. A meta-analysis of 67 studies by Romagnuolo et al. reported that a negative MRCP did not exclude a diagnosis, if the pretest suspicion of malignancy was high, with suspicion only reduced by 10% by a normal MRCP [65].

Similarly, in patients with known hypersensitivity or allergy to contrast agents, or chronic kidney disease, CECT scanning is seldom used. The use of contrast agents is a major limitation to the use of CECT, as CECT formulates a diagnosis of luminal or extraluminal pathology based on enhancement patterns and attenuation value in the portal venous phase. In addition, radiation exposure is another factor that gives MRI/MRCP an edge over CECT for the evaluation of biliary diseases. The increasing use of CECT has heightened concerns about relatively large cumulative exposure to radiation owing to repeated examinations. The average typical effective doses for a basic CT of the abdomen and the chest are 8 mSv and 7 mSv, respectively [66], although the cancer risk is negligible when examined from a population level. Extrapolation of data from lung cancer screening clearly shows that the benefits of using CECT scanning at present outweigh the risks associated with cumulative exposure to radiation [67], provided it is not used for asymptomatic cases.

3.1.8 Cost-effectiveness profile

Performing MRI/MRCP prior to ERCP in planning for a subsequent therapeutic strategy has been shown to be a more cost-effective approach for biliary diseases. Howard et al. reported, in a probabilistic sensitivity analysis, that with a low–moderate probability of bile duct stones in a post-cholecystectomy situation, there was a 59% likelihood of MRCP being a cost-saving procedure, with an 83% chance that MRCP had a cost-effectiveness ratio more favorable than \$50 000 per quality-adjusted life year (QALY) gained [68]. Similar findings were echoed by Vergel et al., wherein MRCP was both cost-effective and showed improved quality of life outcomes, compared with diagnostic ERCP [69].

3.1.9 Environmental impact

A recent systematic review highlighted that the energy consumption of diagnostic radiology devices, such as MRI and CECT scanners, constitutes a significant portion of the overall energy usage in a radiology department [70]. Interestingly, this systematic review reported that a considerable percentage (40%–91%) of the energy consumption of these devices was defined as nonproductive, emphasizing the need to optimize device usage and reduce idle times [70]. Other sustainability actions were shown to be implementing informatic tools for workflow and optimizing operating modes, with estimated annual savings ranging from 14 180 to 171 000 kWh [70]. For MRI, the carbon footprint associated with the entire individual ser-

vice has been measured up to a maximum of 22.4 kg CO₂-equivalents, as Scope 2 and Scope 3 emissions. This value includes both in-hospital process energy (29 kWh per patient) and out-of-hospital energy (about 75 kWh per patient), which is required not only for electricity generation during its medical use but also for the manufacturing of the MRI scanner itself and the disposable and reusable products used during diagnostic activities [71]. Only approximately 28% of the total MRI life-cycle energy is used for image acquisition, suggesting potential improvements to reduce the environmental impact [71].

3.1.10 Certainty of the evidence

The risk of bias assessment for each study can be found in **Table 8s**. Overall, the included studies were considered to be of good quality. The certainty of evidence for all clinical outcomes in this PICO question was downgraded because the evidence was based only on nonrandomized observational studies in the absence of RCTs (**Table 5s**). Therefore, for both the outcomes of diagnostic accuracy for the detection of the obstruction level and of determining the malignant etiology of the stricture, the quality of evidence was rated as low and a conditional recommendation was proposed.

3.2 Distal biliary strictures

RECOMMENDATION 3

ESGE recommends the combination of EUS-guided tissue acquisition and ERCP-based sampling as the preferred diagnostic approach for tissue acquisition in patients with jaundice and distal extrahepatic biliary stricture in the absence of a pancreatic mass.

Strong recommendation, moderate quality evidence.

Tissue sampling to establish the nature of the stenotic lesion is a key step in the diagnostic work-up of biliary strictures. Although these strictures can be due to both extrinsic compression and intrinsic pathologies, the current guideline will be limited to bile duct lesions only.

It is already known that a significant proportion (70%–80%) of biliary strictures are malignant, with the risk of malignancy being higher in patients with a definitive mass on cross-sectional imaging than in those with no clear mass lesion [72]. Early diagnosis is therefore important in directing patients to the proper therapeutic strategy. While transpapillary brush cytology or forceps biopsy after sphincterotomy during ERCP (ERCP-TA) have been the standard sampling modality, EUS-guided tissue acquisition (EUS-TA) has become a useful addition to the diagnostic armamentarium over time. The pooled sensitivities of brush cytology and intraductal biopsies were found to be 45% and 48%, respectively, while the combination of the two only modestly increased the sensitivity to 59% [73]. In contrast, EUS-TA has been reported to have a pooled diagnostic sensitivity of 83% for distal biliary strictures [74]. The appropriate choice of modality will depend not only on the availability of suitable expertise, but also on the location of the lesion and

the presence of jaundice. Indeed, EUS-TA has shown better sensitivity for distal lesions compared with proximal lesions [74]. Moreover, in the absence of jaundice, ERCP-TA should be avoided.

3.2.1 Benefits

The task force performed a meta-analysis of eight studies [75, 76, 77, 78, 79, 80, 81, 82] directly comparing EUS-TA with ERCP-TA for cases requiring additional biliary drainage for jaundice and the characteristics of these studies are outlined in **Table 9s**. EUS-TA performed significantly better than ERCP+brushing (ERCP+brushing vs. EUS-TA: OR 0.31, 95%CI 0.12–0.77; $I^2=75\%$) and with a nonsignificant trend even against ERCP-biopsies (ERCP-TA vs. EUS-TA: OR 0.66, 95%CI 0.38–1.16; $I^2=0\%$) (**Fig. 3s**).

EUS-TA is superior owing to the fact that EUS can enable optimal visualization of the distal bile duct mass or thickening thereby appropriately targeting the lesion. In fact, bile duct masses as small as 5mm or a wall thickness of >3mm have been shown to be best suited for EUS-TA [75, 83]. Moreover, a meta-analysis (10 studies, 1162 patients) has shown that there is a 14% incremental benefit of EUS for achieving the diagnosis after nondiagnostic brush cytology [84]. EUS can aid in tumor staging and access to regional or distant lymph nodes or distant metastases.

The panel analyzed the diagnostic potential of combining the two endoscopic procedures (EUS-TA and ERCP-TA) for biliary stricture, based on three studies [75, 76, 77]. The diagnostic accuracy for the combined approach was 93%–98% compared with 76%–94% and 55%–81% for EUS-TA only and ERCP-TA only, respectively. The combined approach was significantly superior (**Fig. 4s**): EUS-TA+ERCP vs. ERCP-TA alone, OR 6.2, 95%CI 2.7–13.9; $I^2=33\%$; EUS-TA+ERCP vs. EUS-TA alone, OR 2.6, 95%CI 1.4–5.1; $I^2=0\%$).

This strategy of combining EUS and ERCP is likely to help in reducing the grey zone of nondiagnostic or indeterminate biliary strictures, when the diagnostic procedures have to be further optimized; however, a negative report for either EUS-TA or ERCP-TA cannot exclude malignancy as both have low post-test probabilities [84].

3.2.2 Harms

While there are no data directly comparing ERCP-TA with EUS-TA for patients without jaundice, meaning they do not require biliary drainage, we could suggest the use of only EUS-TA over ERCP-TA, given the better performance of EUS-TA and the adverse events (AEs) associated with ERCP, which include post-ERCP pancreatitis, cholangitis, duodenal perforation, and bleeding. Although targeting a thickened stenotic area or mass at the lower end of the bile duct is technically easier, a theoretical risk of penetrating a nondrained biliary system leading to bile leak or intracholedochal bleeding should be considered. Nevertheless, the pooled rate of AEs for EUS-TA for biliary strictures is 1%, with the majority of AEs being mild and self-limiting [74].

Despite the available data, there are certain caveats to its interpretation with respect to current practice. While most of

the EUS-TAs reported in the above-mentioned studies consisted of EUS-guided fine-needle aspirations (EUS-FNAs), it is EUS-FNB needles that are now commonly used worldwide. With the advent of the newer generation of end-cutting biopsy needles, FNB has been found to be superior to FNA [85] in terms of tissue yield. Therefore, with EUS-FNB, the yield of EUS-TA for distal biliary strictures is expected to improve further, although we still need more data. Similarly, needle size and ancillary suction techniques are other areas of contention [86] that might need answers in order to optimize EUS-TA in distal biliary strictures.

3.2.3 Cost-effectiveness profile

The cost-efficacy of combining EUS-TA and ERCP-TA has not been investigated.

3.2.4 Environmental impact

Gastrointestinal endoscopy is an intensive procedure with significant contributions to greenhouse gas emissions [87]. Until studies addressing the ecologic impact of endoscopy in diagnosing distal biliary strictures become available, adherence to guidelines is paramount to assure the lowest possible environmental impact while maintaining a good quality of the medical act [88]. In this regard, audit of the procedural diagnostic yield and maintenance of a good standard of quality in endoscopy also avoids unnecessarily repeating endoscopic procedures and reduces their environmental impact.

3.2.5 Certainty of the evidence

The risk of bias assessment for each study included in the meta-analysis can be found in **Table 10s**. Although based only on retrospective studies, the high quality of the studies, lack of imprecision/indirectness/inconsistency, and, above all, the high magnitude of the effect (OR of the combined diagnostic approach >5 vs. ERCP alone and >2 vs. EUS alone) led to uprating of the level of evidence and the strength of recommendation, as per GRADE policy (**Table 5s**).

RECOMMENDATION 4

ESGE suggests performing EUS and ERCP in the same session as this approach does not increase the risk of adverse events nor impair the effectiveness of the techniques. Conditional recommendation, very low quality of evidence.

Patients with jaundice due to extrahepatic biliary strictures may require both tissue sampling and biliary drainage. There are no dedicated studies comparing the outcomes of the strategy of performing EUS-TA and ERCP separately or in the same session for isolated biliary strictures; however, evidence may be extrapolated from six studies (five retrospective and one RCT) that cover a wide range of benign and malignant pathology, with the majority of lesions being pancreatic masses [89, 90, 91, 92, 93, 94].

3.2.6 Benefits

Table 11s reports the baseline characteristics of these six studies [89,90,91,92,93,94]. On analysis, same-session EUS and ERCP had similar cannulation rates (OR 1.0, 95%CI 0.3–2.9; $I^2 = 11\%$) compared with separate session procedures (**Fig. 5s, part a**). Performing both procedures in the same session has the benefit of improved tissue diagnosis from the combined approach, as mentioned previously.

In the only prospective RCT, 180 patients with suspected distal obstructive jaundice were randomized into three groups: single-session EUS and ERCP, EUS and ERCP in different sessions, and ERCP-only groups [91]. Performing the two procedures in the same session required similar procedure times when compared with separate sessions, while anesthetic and endoscopic complications were similar among all three groups [91]. Aslanian et al. have pointed out that the same-session approach had lower anesthesia requirements [89]. These data tend to favor the combined EUS and ERCP approach, preferably in the same session whenever possible, for reasons of procedural optimization and better patient comfort.

Moreover, where EUS was performed first, it was possible to avoid ERCP in four cases in the study by Chu et al. [91]. Therefore, the EUS findings can be regarded more as a roadmap to better understand the anatomy of the obstructed biliary system and guide the therapeutic endoscopic procedures. Finally, a more expedited patient evaluation, the avoidance of repeated sedation [89], a shorter time to chemotherapy [93], shorter hospitalization, and lower costs [95] are potential benefits of the combined procedures.

3.2.7 Harms

On analysis, same-session EUS and ERCP did not produce an increase in AEs (OR 1.2; 95%CI 0.7–2.0; $I^2 = 20\%$) compared with separate sessions (**Fig. 5s, part b**).

Our analysis did not find differences in the overall AE rate between single and separate sessions for EUS-TA and ERCP; however, the included studies mainly referred to pancreatic masses. For biliary lesions, the risk of AEs may be higher. First, the main pancreatic duct is rarely stenotic in pure biliary lesions, increasing the risk of post-procedural pancreatitis. Second, the smaller size of biliary lesions compared with pancreatic masses and the transbulbar approach that is often used during biliary tumor biopsies make puncture of the lesion more challenging. These harms seem however to be related to the type of lesion and may be independent of the sequence/combination of the two procedures.

Performing EUS-TA and ERCP during the same session may require a longer duration of sedation for the session, potentially resulting in greater use of general anesthesia [89,93]; however, amounts of anesthetic drugs used in the combined procedure seem to be lower than in separate sessions [89,94] and anesthesia-related AEs do not differ between the two strategies [93,94]. Vila et al. reported three desaturations (one requiring orotracheal intubation and one evolving into aspiration pneumonia) in the same-session EUS and ERCP group, and one desaturation in the separate sessions group, with no significant differences found [94].

3.2.8 Cost-effectiveness profile

One retrospective single-center study addressed the cost of combined EUS and ERCP considering the costs of endoscopic instruments, single-use endoscopic devices, anesthetic drugs, procedure duration, and hospitalization days [95]. The authors compared the estimated costs of the single-session strategy with the expected costs of separate sessions, calculating a cost-saving of €510 per patient in the subgroup of patients who underwent single-session EUS-FNA and ERCP for malignant lesions, mainly owing to reduced hospitalization time, procedure duration, and professional fees.

3.2.9 Environmental impact

The coupling of the two procedures in the same session theoretically brings the advantage of lower energy requirements for sedation, postprocedural monitoring, and hospitalization, therefore theoretically this recommendation should decrease the environmental footprint of the endoscopic endeavor in diagnosing distal biliary strictures. However, further studies are necessary to specifically address this issue.

3.2.10 Certainty of the evidence

The risk of bias assessment for each study can be found in **Table 12s**. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that it was mainly noncomparative observational studies that were included (**Table 5s**). For the two outcomes of cannulation rate and AE rate, further downgrading was applied because of imprecision (wide CIs crossing 1), which downgraded the quality of evidence to very low.

RECOMMENDATION 5

ESGE suggests performing EUS in patients with suspected biliary stricture and/or unexplained common bile duct dilatation even in the absence of abnormal laboratory tests. Conditional recommendation, very low quality of evidence.

With the widespread use of high resolution cross-sectional imaging (CECT, MRI, and MRCP), the incidental finding of CBD dilatation without symptoms and with normal liver function tests is being increasingly discovered. A dilated CBD is defined as having a diameter of ≥ 7 mm and is commonly encountered in older people, and those with previous cholecystectomy or chronic narcotic use [96,97,98]. In the absence of any identifiable etiology on imaging, in clinical practice, these patients are usually referred for EUS examination; however, there is scarce literature on the yield of EUS in this setting. Moreover, a further challenging scenario could be the assessment of the ampulla, where flat lesions can be missed during cross-sectional imaging and EUS evaluation. Although evidence in the literature is lacking, the use of side-viewing endoscopes/duodenoscopes for ampullary assessment in patients with distal biliary stricture without a detectable mass could be a useful addition to the diagnostic algorithm in this specific setting.

3.2.11 Benefits

The task force performed a meta-analysis, finding seven retrospective studies and one previous meta-analysis focusing on the diagnostic value of EUS for this indication (**Table 13s**) [99, 100, 101, 102, 103, 104, 105, 106].

The rate of abnormal findings in these studies was 6% to 35%, with the etiologies being mostly benign (CBD stones in a large majority) and very rarely malignant (0%–5% for ampullary and pancreatic tumors). Oppong et al. demonstrated that previous cholecystectomy is significantly associated with negative EUS findings in the group of patients with isolated CBD dilatation ($P=0.005$) [106]. In the study of Kaspy et al., univariate, bivariate, and multivariate logistic regression analyses demonstrated significant negative associations between an EUS finding of CBD stones or sludge with history of cholecystectomy (OR 0.23; $P=0.03$) and age <65 years (OR 0.05; $P=0.03$), with mean age tending to be higher in patients with CBD stones or sludge (78 vs. 66 years; $P=0.07$) [103]. In contrast, they found no association between symptoms (biliary-type abdominal pain) and EUS diagnosis of CBD stone or sludge.

The yield of EUS examination in this setting was evaluated in a systematic review and meta-analysis by Chhoda et al. that included eight full manuscript studies and three conference abstracts [99]. Among 224 asymptomatic patients with CBD dilatation, the cumulative yield of EUS for any pathology was 11% (95%CI 4%–22%) [99]. The EUS yield for benign etiologies was 9% (95%CI 1%–22%), including choledocholithiasis (3%, 95%CI 0%–11%), whereas for malignant pathology it was 5% (95%CI 0%–3%) [99].

The meta-analysis of the available data showed a rate of abnormal findings of 15% (95%CI 9%–21%), whereas the rate of malignancy was <0.1% (95%CI 0%–0.1%) (**Fig. 6s**).

Despite their limitations (retrospective single-center design, limited sample size, and heterogeneity of the outcome measures), all these studies showed a low, but not insignificant, rate of benign abnormal conditions (most commonly CBD stones) during endosonographic exploration of asymptomatic biliary dilatation, demonstrating the potential benefit of performing EUS in patients with suspected biliary stricture even in the absence of abnormal laboratory tests. Based on the evidence above, the panel suggests the use of EUS in this setting, even though neoplastic conditions are extremely rare.

3.2.12 Harms

No AEs were reported in patients undergoing EUS exploration for suspected biliary structures with normal laboratory tests. Diagnostic EUS is considered a low risk procedure, with rare complications such as bacteremia, bleeding, duodenal perforation, and sedation-related complications, comparable with that of diagnostic upper gastrointestinal endoscopy [107] and must be factored against the diagnostic yield of EUS, after shared decision-making with the patient.

3.2.13 Cost-effectiveness profile

Despite its resource use, EUS seems cost-effective for this indication by avoiding additional imaging examinations when no pathologic finding is detected.

3.2.14 Environmental impact

In a context where the rate of malignancy is <0.1% (as presented above), justification for a resource-intensive endoscopic procedure that is a generator of greenhouse gasses and waste is easily debatable. Because appropriateness criteria are not perfect, they should always be combined with clinical judgment, with case-by-case analysis and decision-making warranted in this context [88].

3.2.15 Certainty of the evidence

The risk of bias assessment for each study can be found in **Table 14s**. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that there were only noncomparative observational studies included (**Table 5s**). For the two outcomes of pooled malignancy rate and rate of abnormal findings, further downgrading was applied because of inconsistency (high heterogeneity), so downgrading the quality of evidence to very low.

3.3 Perihilar biliary strictures

RECOMMENDATION 6

ESGE suggests that brushing cytology should be completed along with fluoroscopy-guided biopsies, wherever technically feasible, in patients with perihilar biliary strictures.

Conditional recommendation, low quality of evidence.

A recent meta-analysis of 21 observational studies [108] concluded that fluoroscopy-guided biopsies plus brush cytology during ERCP for the evaluation of biliary strictures could lead to a 20% increased diagnostic yield (95%CI 9%–31%) for malignancy versus brush cytology alone. Moreover, the combination of fluoroscopy-guided biopsies and brush cytology was associated with the highest sensitivity (66%, 95%CI 63%–69%) compared with brush cytology alone (40%, 95%CI 37%–43%) and fluoroscopy-guided biopsies alone (52%, 95%CI 49%–56%). Of interest, this analysis included both proximal and distal strictures with no difference found between them in terms of outcome on subgroup analysis. It should be acknowledged that intraductal fluoroscopy-guided biopsies are more demanding and technically challenging, asking for advanced expertise. In addition, one should keep in mind that intraductal biopsies carry a risk of complications such as bleeding, duodenal or bile duct perforation, and pancreatitis, and so, whenever possible, previous multidisciplinary team discussion is recommended in order to decide on the optimal approach.

3.3.1 Benefits

The panel did not identify any RCTs evaluating cytology brushing versus fluoroscopy-guided biopsies, or their combination for proximal biliary strictures. Two cohort studies [109, 110] comparing the efficacy of brushing, fluoroscopy-guided biopsies, and their combination for proximal biliary strictures were retrieved (**Table 15s**). In the first study, 58 patients with hilar

CCA were included and the sensitivities of brushing cytology, fluoroscopy-guided biopsies, and their combination were 41%, 53%, and 60%, respectively [109]. In the second study, 43 patients with proximal biliary strictures were enrolled and underwent both cytology brushing and fluoroscopy-guided biopsies using a particular double-balloon enteroscopy forceps that was advanced to the point of interest through a plastic pusher after removal of the guidewire [110]. The sensitivity of brushing cytology was 49%, but was 69% for fluoroscopy-guided biopsies, and increased to 80% when both methods were combined.

The meta-analysis of these two studies showed an incremental diagnostic yield of 25% (95%CI 11%–38%; $P<0.001$; $I^2=0\%$) (**Fig. 7s, part a**) and a significantly increased sensitivity (OR 2.7, 95%CI 1.5–4.9; $P<0.001$; $I^2=0\%$) (**Fig. 7s, part b**) for diagnosing malignancy when adding fluoroscopy-guided biopsies to brushings in perihilar biliary strictures.

Transpapillary biopsies can be performed with standard biopsy forceps. Nevertheless, studies evaluating slim forceps with a design that allows the angle of the forceps to be modified have shown good results [111,112] that appear to be even better than those obtained with conventional biopsy forceps [113].

Some reports have shown an increase in diagnostic yield with an increasing number of biopsies: in a retrospective study, after three or more biopsies, a sensitivity of 100% was found [114] and, in a prospective study of 31 patients, the reported sensitivity was 55% after three biopsies, and 59% after four or more biopsies [115]. However, in the most recent meta-analysis available, when comparing the 13 studies that reported the number of biopsies taken in each study, there was no difference in sensitivity between studies that performed fewer than four biopsies and studies that performed four or more biopsies (69% vs. 70%) [116]. Therefore, three to four biopsies may be an adequate number.

Several technical variants have been described to facilitate the ascent of the biopsy forceps through the bile duct with good results. Although the evidence comes from small series, given the difficulty of access and lower diagnostic yield in biliary strictures with more proximal locations, it may be useful to use guidance systems to reach such strictures [117,118,119,120].

Studies of dilation of the stenosis prior to biopsy are scarce and, although it appears to increase diagnostic yield without increasing complications, there are insufficient data to recommend its routine use [121,122].

The evaluation of different brushes over several studies has not shown a significant increase in diagnostic performance that would justify the use of any biliary brushes other than the conventional ones [123,124,125].

Recent data from a multicenter RCT with more than 400 included patients showed that the sensitivity of cytology increased with the number of the brush passes [126]. In this study, the sensitivities were 38%, 47%, and 57% when 10, 20, and 30 brush passes were performed, respectively. These results encourage increasing the number of brush passes beyond 10, as this measure would barely increase procedural

time and AEs, and would improve the diagnostic performance of the technique.

3.3.2 Harms

The previously mentioned meta-analysis of studies with both proximal and distal strictures [108] did not find any significant difference in the rate of AEs between the two groups (OR 0.53, 95%CI 0.14–2.05); overall, the number of AEs was low, allowing both techniques to be considered safe to perform. However, two cases with severe AEs including bleeding and perforation have been described in the setting of intraductal biopsies [127,128], so the panel calls for cautious implementation by experienced physicians only, especially when considering that proximal strictures may be more difficult to approach, requiring higher technical skills to manipulate and advance the biopsy forceps.

3.3.3 Cost-effectiveness profile

One cost-utility analysis comparing five different sampling techniques among patients with suspected CCA and PSC did not reveal any significant difference between brushing and biopsy forceps sampling in terms of incremental QALYs and cost [129]. However, one could reasonably assume that, when both modalities are combined, it could lead to an increased procedural cost.

3.3.4 Environmental impact

It is known that processing of biopsy/cytology samples obtained during endoscopy leads to high greenhouse gas emissions; however, this is an unavoidable process. Despite the fact that combining two sampling modalities (brushing and biopsy forceps) in cases of proximal biliary strictures would definitely increase the environmental impact of the procedure as two devices and two specimen pots should be used, one cannot oversee the potential benefit of avoiding a second ERCP following a positive result after combining the two methods. Therefore, appropriate patient selection after evaluation by cross-sectional imaging remains crucial for minimizing the environmental impact of the procedure [87,130].

3.3.5 Certainty of evidence

The risk of bias assessment for each study can be found in **Table 16s**. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that there were only observational studies included (**Table 5s**). Therefore, the panel concluded by making a conditional recommendation with a low quality of evidence.

RECOMMENDATION 7

ESGE suggests EUS-TA for perihilar strictures when ERCP-based modalities yield insufficient results, provided that curative resection is not feasible and/or when cross-sectional imaging has shown accessible extraluminal disease.

Conditional recommendation, low quality of evidence.

The combination of ERCP-based brush cytology and forceps biopsies provides high specificity in the diagnosis of perihilar strictures, but may yield insufficient results in a significant proportion of patients, culminating in a low diagnostic sensitivity. EUS-TA has proven useful in increasing the diagnostic yield. Although it is regarded as safe with low overall complication rates (<1%) and carries a low risk of bile leakage during EUS-FNA for biliary strictures (2.6%) [131], some specific considerations apply to patients with perihilar disease.

3.3.6 Benefits

A single-blinded comparative study confirmed superior sensitivity and diagnostic accuracy for EUS-FNA in suspected malignant biliary strictures, compared with ERCP-based brush cytology + forceps biopsies (94% and 94% vs. 50% and 53%, respectively) [79], results that are in line with more recent studies on the topic [76, 132]. In the context of perihilar disease in particular, one of the first prospective studies evaluating the yield of EUS-FNA in surgical patients with negative brush cytology ($n = 44$) was published in 2004 and showed high diagnostic accuracy (91%) and sensitivity (89%) [133]. Most importantly, EUS and EUS-FNA changed the surgical approach in almost two-thirds of patients, without resulting in complications.

When comparing the diagnostic accuracy of EUS-TA in perihilar and distal strictures however, significant differences in sensitivity and negative predictive value have surfaced. A 2020 prospective evaluation of EUS-FNA in the diagnosis of biliary strictures ($n = 97$; 46% hilar) showed an overall sensitivity of 75% (95%CI 64%–84%), with subgroup sensitivity and negative predictive value reaching 95% and 93% for distal lesions without stenting, but being much lower (56% and 33%, respectively) in patients with stented perihilar lesions [134]. While it should be noted that only early generation 22–25G FNA needles were used in this study, hilar location, underlying PSC, and previous stenting were all identified as independent risk factors for inaccurate histologic diagnosis using EUS-TA.

Lower EUS-FNA sensitivity in proximal CCA has been reproduced in several studies. Differences in tumor biology, absence in hypoechogenic mass-like appearance, and diffuse axial growth patterns may complicate successful identification of the proximal lesion itself [135, 136]. Although no comparisons between distal and proximal strictures exist to date, it has been suggested that contrast-enhanced harmonic EUS might increase T-staging adequacy [132, 137]. A previous meta-analysis [138] found a 15% (95%CI 9%–24%) incremental benefit of EUS after inconclusive ERCP with brushing; however, in this study, patients with both proximal and distal strictures were included. Moreover, in a recent meta-analysis of 11 studies including patients with both perihilar and proximal strictures, the pooled sensitivity of ERCP alone with any tissue acquisition method and EUS alone did not differ (70% [95%CI 66%–73%] vs. 74% [71%–77%]; $P = 0.31$) [139].

The studies evaluating the role of EUS in the diagnosis of perihilar strictures are presented in **Table 17s**. The pooled rates of sensitivity and diagnostic accuracy were 78% (95%CI 70%–86%; $I^2 = 76\%$) and 84% (95%CI 78%–91%; $I^2 = 46\%$), respectively. The task force identified only two comparative studies [76, 77] that

compared EUS-TA and ERCP with brush cytology for patients with perihilar strictures. The meta-analysis of these two studies showed an incremental diagnostic yield for adding EUS-TA to ERCP of 33% (95%CI 15%–50%; $P < 0.001$; $I^2 = 0\%$) (**Fig. 8s**).

3.3.7 Harms

Peritoneal seeding and subsequent iatrogenic upstaging are theoretical, yet clinically significant, limitations of EUS-TA and should be weighed against their potential diagnostic benefit. Even more so, EUS-TA for CCA has been wielded as a contraindication for liver transplantation [135]. The clear majority of published cases are however limited to needle tract recurrences in the context of pancreatic adenocarcinoma [140] or following radiofrequency ablation for hepatic lesions [141]. A Japanese nationwide survey suggested an incidence rate of 0.33% in the context of PDAC, with a significantly higher rate of needle tract recurrences in patients with PDAC who had undergone transgastric EUS-TA (0.86%) [142]. A pattern that might be explained by the needle tract location lying beyond the surgical resection margins.

Several retrospective series have evaluated the risk of peritoneal carcinomatosis following EUS-FNA in the context of PDAC, where it seems to outperform percutaneous FNA (2% vs. 16%) [143] and no differences were seen when comparing EUS-FNA with alternative methods of tissue acquisition [144, 145]. A recent meta-analysis of 10 studies (13 238 patients) showed that the pooled rate of needle tract seeding after EUS-TA of pancreatic lesions was 0.3% (95%CI 0.2%–0.4%) and no difference was observed in terms of metachronous peritoneal dissemination between patients who underwent EUS-TA and nonsampled patients (OR 1.0, 95%CI 0.7–1.5; $P = 0.31$), thereby confirming the low risk of seeding with this procedure [146].

Little evidence on EUS-TA-related peritoneal seeding is available in hilar CCA, with one specifically designed retrospective study ($n = 150$) showing no significant impact of needle passes on overall or progression-free survival [147]. A comparative study in patients with CCA undergoing transperitoneal FNA before neoadjuvant chemoradiotherapy and liver transplantation showed higher rates of peritoneal metastasis (83%) in patients with a positive transperitoneal FNA [148]. The risk of needle tract seeding seems higher however following a percutaneous approach than with EUS [143], making application of these recommendations to EUS-TA more difficult.

While data on exclusively proximal strictures are lacking, a recent meta-analysis of studies with both proximal and distal strictures showed that EUS-TA was associated with significantly fewer AEs compared with ERCP-based sampling (OR 8.1, 95%CI 3.0–22.3), with minor bleeding being the main EUS-associated AE [139].

3.3.8 Cost-effectiveness profile

While the cost of EUS with FNA/FNB varies across Europe depending on the local market, ERCP resulted in 9.05 QALYs and a cost of \$34 685, for a cost-effectiveness ratio of \$3832, while EUS resulted in an incremental increase of 0.13 QALYs and \$2773, for an incremental cost-effectiveness ratio (ICER) of \$20 840 per QALY gained [40].

3.3.9 Environmental impact

There are no data about the potential environmental footprint of EUS-TA for proximal strictures; however, the ecologic burden of an additional procedure should be taken into account (endoscope reprocessing, use of FNA/FNB, sample processing, and other aspects). Furthermore, as for every endoscopic procedure, the presence of an appropriate indication to avoid unnecessary examinations should be recorded prior to the examination [88].

3.3.10 Certainty of evidence

The risk of bias assessment for each study can be found in **Table 18s**. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that there were only observational studies included (**Table 5s**). Therefore, the panel concluded by making a conditional recommendation with a low quality of evidence.

3.4 Intraductal Imaging

RECOMMENDATION 8

ESGE suggests using standard ERCP diagnostic modalities at index ERCP. In the case of indeterminate biliary strictures, ESGE suggests taking cholangioscopy-guided biopsies, in addition to the standard ERCP diagnostic modalities. Additional intraductal biliary imaging modalities can be selectively used, based on clinical context, local expertise, and resource availability. Conditional recommendation, very low quality of evidence.

The interpretation of real-time images during cholangioscopy may aid in distinguishing between benign and malignant strictures. Malignant lesions typically appear as either nodular, papillary, or infiltrating masses. Nodular masses usually lead to luminal obstruction and exhibit irregular mucosa with pronounced neovascularization. Papillary masses, on the other hand, feature numerous papillary projections and less neovascularization, while infiltrating masses cause luminal narrowing without a distinct mass, but display more whitish mucosal discoloration and neovascularization [149].

The documented sensitivity of visual assessment for identifying malignancy in strictures varies from 64% to 95% [149, 150], with most evidence on cholangioscopy being derived from clinical experiences with single-operator cholangioscopy (SOC). In fact, while other cholangioscopy methods, such as direct cholangioscopy and the dual-operator mother–baby technique, may be employed selectively depending on the clinical scenario, local proficiency, and resource availability, SOC should be regarded as the preferred technique for cholangioscopy (**Table 19s**). In terms of visual assessment performance, image quality has improved over the last few years, and artificial intelligence-based systems have been specifically trained with SOC images [151, 152], potentially enabling the avoidance of significant interobserver variation, and/or targeting biopsies. Nevertheless, further study is required to assess the utility

of artificial intelligence before a recommendation can be issued.

Endoscopic impressions alone are therefore not considered a recognized standard for making oncologic or other critical decisions. The primary utility of cholangioscopy lies in tissue acquisition; however, recognizing the distinguishing features of malignant strictures can facilitate the targeting of cholangioscopy-guided biopsies, potentially enhancing the diagnostic efficacy of this technique.

Alternative methods for assessing biliary strictures, including intraductal ultrasound (IDUS) and confocal laser endomicroscopy (CLE), are still evolving and have not established a concrete role in clinical practice. IDUS findings suggestive of malignancy include eccentric wall thickening, destruction of wall layers, intraluminal mass with irregular margins possibly invading surrounding tissue, and heterogeneous lesions with uneven mucosal surfaces [152,153,154]. Similarly, CLE employs slender confocal laser probes inserted through the duodenoscope's working channel, and malignant strictures manifest as thick dark bands of collagen fibrils and thickened white bands within vessels [155]. Both IDUS and CLE have been shown to improve sensitivity in diagnosing malignant strictures when compared with ERCP alone; however, these procedures are costly and require considerable skill to master, with an anticipated low level of interobserver agreement, thereby impeding their widespread adoption in the near future.

3.4.1 Benefits

Focusing on cholangioscopy, our de novo literature search identified 12 studies (including one RCT) (**Table 20s**) assessing the diagnostic performances of standard ERCP diagnostic modalities, including fluoroscopy-guided biopsies with/without brush cytology, compared with ERCP with cholangioscopy [80, 156,157,158].

The analysis revealed that the incremental yield of cholangioscopy-guided biopsies was 27% (95%CI 10%–45%), with a significant superiority compared with standard ERCP ($P=0.002$; $I^2=62\%$) (**Fig. 9s**). Furthermore, the sensitivity of ERCP with cholangioscopy was notably higher than standard ERCP (74% [95%CI 62%–86%] vs. 50% [28%–72%]; OR 1.1, 95%CI 1.0–1.3; $I^2=64\%$) (**Fig. 10s**). In the case of biliary strictures of undetermined etiology despite previous ERCP with standard diagnostic modalities (indeterminate biliary strictures), given the incremental sensitivity yield, patients should be referred to specialized tertiary centers for cholangioscopy.

3.4.2 Harms

In our meta-analysis, no disparities between cholangioscopy and standard ERCP were found in terms of risk of AEs (OR 1.5, 95%CI 0.8–2.5; $I^2=0\%$) (**Fig. 11s**), with pancreatitis and cholangitis being the most frequently reported. In this regard, the evidence regarding the potential benefits of antibiotic prophylaxis for preventing post-endoscopy cholangitis in cholangioscopy is limited, retrospective, and conflicting [159,160,161,162,163]. Of note, one study reported that the additional time required for cholangioscopy during ERCP was around 14 minutes (95%CI 10–20 minutes) [157]. Moreover, access to cholan-

gioscopy remains largely confined to tertiary referral centers with endoscopists specifically trained in intraductal biliary imaging modalities.

3.4.3 Cost-effectiveness profile

One study detected an additional expense of \$2637 when incorporating cholangioscopy into ERCP [164]; however, it has been shown that, in selected cases, cholangioscopy yields cost-effective outcomes, reducing the need for multiple procedures and associated expenses in diagnosing malignancies. In fact, when assessing the economic ramifications of endoscopy procedures and hospital admissions necessary for the diagnosis and management of indeterminate biliary strictures, with and without the use of SOC, the implementation of cholangioscopy demonstrated cost-effectiveness, resulting in a reduction in both the number of procedures (relative reduction of 31%) and associated costs (decrease of €13000, representing a relative variation of 5%) when compared with standard ERCP [164].

3.4.4 Environmental impact

There are no data about the potential environmental footprint of cholangioscopy for biliary strictures. Waste production derived from the use of disposable devices and endoscopes (i.e. single-use cholangioscopes) is one of the main sources of direct carbon emissions in endoscopy [165]. Therefore, combining cholangioscopy with standard ERCP would increase the environmental impact of the procedure. Moreover, an adjunctive sampling modality (cholangioscopy-guided biopsies) would translate into further increases in the indirect sources of emissions derived from processing of histologic samples. On the other hand, the incremental sensitivity yield of cholangioscopy compared with standard ERCP may lead to a reduction in the number of unnecessary re-examinations, with theoretical benefit in terms of avoiding procedure-related sources of direct carbon emission, and indirect sources such as unnecessary patient transportation [87].

3.4.5 Certainty of the evidence

The risk of bias assessment for each study can be found in **Table 21s**. The certainty of evidence for all clinical outcomes in this PICO question was downgraded because it was based mainly on nonrandomized studies (**Table 5s**). For the two outcomes of incremental yield and AE rate, further downgrading was applied owing to indirectness (heterogeneity in the standard ERCP modalities for tissue sampling), so downgrading the quality of evidence to very low.

4 Unmet needs and evidence gaps

The ESGE commissioned this guideline on diagnostic work-up of biliary strictures to facilitate the appraisal of the published evidence on tumor markers, distal and perihilar strictures, and intraductal imaging to provide recommendations and compact, up-to-date literature to support the statements. Unfortunately, most of the literature is based mainly on the use of the diagnostic techniques for pancreatic masses, and isolated data

on biliary stricture are scarce and frequently based on subgroup analyses of other studies.

As is evident above, the majority of the recommendations in this Guideline are based on low quality evidence owing to the lack of RCTs on these topics. The low quality of the evidence points to the pressing need for prospective studies and RCTs in this field. Various unmet needs, such as for distal stricture (data on third generation, end-cutting EUS-FNB needles for tissue acquisition) and for perihilar stricture (data on EUS-FNB versus cholangioscopy-guided biopsies), still need to be addressed in the literature. More data are also needed about methods to improve and implement the handling of cytopathology after tissue sampling, and about the addition of more advanced techniques such as next generation sequencing in this field. Liquid biopsies and the analysis of portal vein circulating cells potentially represent interesting research fields that need to be further developed and investigated, given the promising preliminary results. Moreover, in recent times, artificial intelligence has forged its way into routine endoscopy practice, and studies to incorporate its use for the diagnosis of biliary stricture are scarce. Furthermore, the role of green endoscopy, including the impact of imaging and use of endoscopy equipment on the environment, is another uncovered area in this topic.

Disclaimer

ESGE Guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply to all situations and should be interpreted in the setting of specific clinical scenarios and resource availability. They are intended to be an educational tool to provide information that may support endoscopists in providing care to patients.

They are not rules and should not be used either to replace clinical judgement or to establish a legal standard of care.

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Conflict of Interest

M. Arvanitakis has received lecture fees from Boston Scientific (2024 ongoing). M. Bronswijk's department has received trial support from Boston Scientific (2021 ongoing). T. Beyna has received consultancy and lecture fees from Olympus, Boston Scientific, and MicroTech, and lecture fees from Cook (all ongoing); his department has received research support/grants from Olympus, Boston Scientific, MicroTech, and Cook. M. Ellrichmann has received consultancy fees from Boston Scientific (2015 ongoing) and MicroTech (2023 ongoing). I. Hritz has received consultancy and training fees from Olympus (2018 ongoing) and consultancy and speaker's fees from MicroTech (2023 ongoing). M. Spadaccini has received speaker's fees from Boston Scientific (2023–2024). G.J.M. Webster has received support for teaching (2010–2024). S.F. Crinò, J. Dhar, A. Facciorusso, R. Gincul, P. Gkolfakis, L. Kylänpää, B. Martinez-Moreno, M. Pezzullo, M. Rimbis, J. Samanta, K. Triantafyllou, R.L.J. van Wanrooij declare that they have no conflicts of interest.

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Diagnostic work-up of bile duct strictures: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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Table 1s PICO questions (population, intervention, comparator, outcome)

PICO question no.	Population	Intervention	Comparator	Outcomes
1	Patients with biliary strictures	CEA, CA 19-9	Not available	• Accuracy for malignancy of the biliary stricture
2	Patients with biliary strictures	MRI/MRCP	CECT-scan	• Accuracy for detection of the level of obstruction • Accuracy for detection of the malignancy
3	Patients with extrahepatic biliary strictures and jaundice	EUS-guided tissue acquisition	ERCP-guided tissue acquisition	• Diagnostic accuracy
4	Patients with extrahepatic biliary strictures requiring EUS-TA and ERCP	EUS and ERCP performed during the same session	EUS and ERCP performed in separate sessions	• Adverse event rate • Bile duct cannulation rate
5	Patients with biliary strictures of unclear etiology and with normal liver function tests	EUS	Not available	• Rate of abnormal findings • Rate of malignant findings

6	Patients with perihilar biliary strictures	ERCP with brush cytology+fluoroscopy-guided biopsies	ERCP with brushing	• Incremental diagnostic yield • Diagnostic sensitivity
7	Patients with perihilar biliary strictures	EUS-guided tissue acquisition+ERCP-guided tissue acquisition	ERCP-guided tissue acquisition	• Incremental diagnostic yield
8	Patients with indeterminate biliary strictures	ERCP with cholangioscopy	Standard ERCP modalities	• Incremental yield • Sensitivity • Adverse event rate

Table 2s. Literature search

Search strategy for PICO1 Search date: Feb 28, 2024 Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present; Embase.com (Elsevier) (1947 to 2024 Feb 28; Wiley Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)] Limits: English, Human Exclusions: letters, notes, comments, editorials, case reports, reviews Ovid MEDLINE ALL 1 exp Bile Ducts/ use ppez 2 exp Bile Duct Neoplasms/ use ppez 3 (bile duct* or biliary or hilar or peri?hilar or klatskin).ti,ab,kf,kw. 4 or/1-3 5 exp Constriction, Pathologic/ use ppez 6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage).ti,ab,kf,kw. 7 5 or 6 8 4 and 7 9 exp Cholestasis/ use ppez 10 cholestasis.ti,ab,kf,kw. 11 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)).ti,ab,kf,kw. 12 or/8-11 13 exp laboratory tests, primary sclerosing cholangitis ppez or exp biliary tract malignancies/ use ppez 14 (Ca-19-9* or CEA* or IgG4* or bilirubin).ti,ab,kf,kw. 15 13 or 14

16 12 and 15
17 animals/ not (humans/ and animals/)
18 16 not 17
19 limit 18 to english language
20 (case reports or comment or editorial or letter).pt.
21 Case Report/
22 19 not (20 or 21)
23 limit 22 to dt=20190530-20211231

Embase.com (Elsevier)
Searches
1 'bile duct'/exp
2 'bile duct tumor'/exp
3 (bile duct* OR biliary OR hilar OR peri?hilar OR klatskin):ti,ab,kw
4 #1 OR #2 OR #3
5 'stenosis, occlusion and obstruction'/exp
6 (constriction OR stricture* OR stenos?s OR obstruction OR occlusion OR blockage):ti,ab,kw
7 #5 OR #6
8 #4 AND #7
9 cholestasis/exp
10 cholestasis:ti,ab,kw
11 (('bile duct*' OR biliary OR hilar OR peri?hilar OR klatskin) NEAR/1 (carcinoma* OR adenoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR cholangiocarcinoma* OR malignanc* OR stricture* OR obstruction OR occlusion OR stenos?s OR blockage OR primary sclerosing cholangitis)):ti,ab,kw
12 #8 OR #9 OR #10 OR #11
13 'laboratory tests'/exp
14 (CA 19-9* OR CEA* OR IgG4* OR bilirubin):ti,ab,kw
15 #13 OR #14
16 #12 AND #15
17 animals/exp NOT (humans/exp AND animals/exp)
18 #16 NOT #17

19 #18 AND English:la
 20 'case reports':it OR comment:it OR editorial:it OR letter:it OR note:it
 21 'Case Report'/de
 22 #19 NOT (#20 OR #21)
 23 #22 AND [30-05-2019]/sd

Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)] - Wiley

#1 [mh "Bile Ducts"]
 #2 [mh "Bile Duct Neoplasms"]
 #3 (bile duct* or biliary or hilar or peri?hilar or klatskin)
 #4 #1 or #2 or #3
 #5 [mh "Constriction, Pathologic"]
 #6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage)
 #7 #5 or #6
 #8 #4 and #7
 #9 cholestasis
 #10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage or primary sclerosing cholangitis))
 #11 #8 or #9 or #10
 #12 CA 19-9* or CEA* or IgG4* or bilirubin
 #13 #11 and #12
 Date added to CENTRAL trials database: May 30, 2019 - present

Final results after duplicate exclusion and exclusion of studies not fulfilling inclusion criteria: 15

Search strategy for PICO2

Search date: Feb 28, 2024

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present; Embase.com (Elsevier) (1947

to 2024 Feb 28; Wiley Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)]

Limits: English, Human

Exclusions: letters, notes, comments, editorials, case reports, reviews

Ovid MEDLINE ALL

1 exp Bile Ducts/ use ppez

2 exp Bile Duct Neoplasms/ use ppez

3 (bile duct* or biliary or hilar or peri?hilar or klatskin).ti,ab,kf,kw.

4 or/1-3

5 exp Constriction, Pathologic/ use ppez

6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage).ti,ab,kf,kw.

7 5 or 6

8 4 and 7

9 exp Cholestasis/ use ppez

10 cholestasis.ti,ab,kf,kw.

11 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)).ti,ab,kf,kw.

12 or/8-11

13 exp MRI, MRCP ppez or exp CECT ppez

14 (MRI* or MRCP* or cholangiograph* or CECT).ti,ab,kf,kw.

15 13 or 14

16 12 and 15

17 animals/ not (humans/ and animals/)

18 16 not 17

19 limit 18 to english language

20 (case reports or comment or editorial or letter).pt.

21 Case Report/

22 19 not (20 or 21)

23 limit 22 to dt=20190530-20211231

Embase.com (Elsevier)

Searches

1 'bile duct'/exp

2 'bile duct tumor'/exp

3 (bile duct* OR biliary OR hilar OR peri?hilar OR klatskin):ti,ab,kw

4 #1 OR #2 OR #3

5 'stenosis, occlusion and obstruction'/exp

6 (constriction OR stricture* OR stenosis OR obstruction OR occlusion OR blockage):ti,ab,kw

7 #5 OR #6

8 #4 AND #7

9 cholestasis/exp

10 cholestasis:ti,ab,kw

11 (('bile duct*' OR biliary OR hilar OR peri?hilar OR klatskin) NEAR/1 (carcinoma* OR adenoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR cholangiocarcinoma* OR malignanc* OR stricture* OR obstruction OR occlusion OR stenosis OR blockage)):ti,ab,kw

12 #8 OR #9 OR #10 OR #11

13 'abdominal imaging'/exp

14 (MRI* OR MRCP* OR cholangiograph* OR CECT):ti,ab,kw

15 #13 OR #14

16 #12 AND #15

17 animals/exp NOT (humans/exp AND animals/exp)

18 #16 NOT #17

19 #18 AND English:la

20 'case reports':it OR comment:it OR editorial:it OR letter:it OR note:it

21 'Case Report'/de

22 #19 NOT (#20 OR #21)

23 #22 AND [30-05-2019]/sd

Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)] - Wiley

#1 [mh "Bile Ducts"]

#2 [mh "Bile Duct Neoplasms"]

#3 (bile duct* or biliary or hilar or peri?hilar or klatskin)
 #4 #1 or #2 or #3
 #5 [mh "Constriction, Pathologic"]
 #6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage)
 #7 #5 or #6
 #8 #4 and #7
 #9 cholestasis
 #10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage))
 #11 #8 or #9 or #10
 #12 MRI* or MRCP* or Cholangiograph* or CECT
 #13 #11 and #12
 Date added to CENTRAL trials database: May 30, 2019 - present

Final results after duplicate exclusion and exclusion of studies not fulfilling inclusion criteria: 11

Search strategy for PICOs 3-4-5-7

Search date: Feb 28, 2024

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present; Embase.com (Elsevier) (1947 to 2024 Feb 28; Wiley Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)]

Limits: English, human

Excluded: letters, notes, comments, editorials, case reports, reviews

Ovid MEDLINE ALL

Searches

1 exp Bile Ducts/ use ppez

2 exp Bile Duct Neoplasms/ use ppez

3 (bile duct* or biliary or hilar or peri?hilar or klatskin).ti,ab,kf,kw.
 4 or/1-3
 5 exp Constriction, Pathologic/ use ppez
 6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage).ti,ab,kf,kw.
 7 5 or 6
 8 4 and 7
 9 exp Cholestasis/ use ppez
 10 cholestasis.ti,ab,kf,kw.
 11 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)).ti,ab,kf,kw.
 12 or/8-11
 13 *Endosonography/ use ppez
 14 *Biopsy, Fine-Needle/ use ppez
 15 (eus or FNA or fine needle or (endoscop* adj2 ultraso*) or endosonograph*).ti,ab,kf,kw.
 16 or/13-15
 17 12 and 16
 18 animals/ not (humans/ and animals/)
 19 17 not 18
 20 limit 19 to english language
 21 (case reports or comment or editorial or letter).pt.
 22 Case Report/
 23 20 not (21 or 22)
 24 limit 23 to dt=20190530-20211231

 Embase.com (Elsevier)
 # Searches
 1 'bile duct'/exp
 2 'bile duct tumor'/exp
 3 (bile duct* OR biliary OR hilar OR peri?hilar OR klatskin):ti,ab,kw
 4 #1 OR #2 OR #3

5 'stenosis, occlusion and obstruction'/exp
 6 (constriction OR stricture* OR stenosis OR obstruction OR occlusion OR blockage):ti,ab,kw
 7 #5 OR #6
 8 #4 AND #7
 9 cholestasis/exp
 10 cholestasis:ti,ab,kw
 11 (('bile duct*' OR biliary OR hilar OR peri?hilar OR klatskin) NEAR/2 (carcinoma* OR adenoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR cholangiocarcinoma* OR malignanc* OR stricture* OR obstruction OR occlusion OR stenosis OR blockage)):ti,ab,kw
 12 #8 OR #9 OR #10 OR #11
 13 'endoscopic ultrasonography'/de
 14 'fine needle aspiration biopsy'/de
 15 (eus OR FNA OR fine needle OR (endoscop* NEAR/2 ultraso*) OR endosonograph*):ti,ab,kw
 16 #13 OR #14 OR #15
 17 #12 AND #16
 18 animals/exp NOT (humans/exp AND animals/exp)
 19 #17 NOT #18
 20 #19 AND English:la
 21 'case reports':it OR comment:it OR editorial:it OR letter:it OR note:it
 22 'Case Report'/de
 23 #20 NOT (#21 OR #22)
 24 #23 AND [30-05-2019]/sd

Cochrane Library [Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL)] - Wiley

ID Search Hits

#1 [mh "Bile Ducts"]
 #2 [mh "Bile Duct Neoplasms"]
 #3 (bile duct* or biliary or hilar or peri?hilar or klatskin):ti,ab
 #4 #1 or #2 or #3
 #5 [mh "Constriction, Pathologic"]

#6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage):ti,ab
 #7 #5 or #6
 #8 #4 and #7
 #9 cholestasis:ti,ab
 #10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) NEAR/2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)):ti,ab
 #11 #8 or #9 or #10
 #12 [mh Endosonography]
 #13 [mh "Biopsy, Fine-Needle"]
 #14 (eus or FNA or fine needle or (endoscop* near/2 ultraso*) or endosonograph*):ti,ab
 #15 #12 or #13 or #14
 #16 #11 and #15
 Date added to CENTRAL trials database: May 30, 2019 – present

Final results after duplicate exclusion and exclusion of studies not fulfilling inclusion criteria: 23

Search strategy for PICO 6:

Search date: Feb 28, 2024

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present; Embase.com (Elsevier) (1947 to 2024 Feb 28; Wiley Cochrane Library [Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL)]

Limits: English, human

Excluded: letters, notes, comments, editorials, case reports, reviews

Ovid MEDLINE ALL

1 exp Bile Ducts/ use ppez

2 exp Bile Duct Neoplasms/ use ppez

3 (bile duct* or biliary or hilar or peri?hilar or klatskin).ti,ab,kf,kw.
 4 or/1-3
 5 exp Constriction, Pathologic/ use ppez
 6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage).ti,ab,kf,kw.
 7 or/5-6
 8 4 and 7
 9 cholestasis.ti,ab,kf,kw.
 10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)).ti,ab,kf,kw.
 11 or/8-10
 12 exp Cytodiagnosis/ use ppez
 13 exp Cytological Techniques/ use ppez
 14 *Specimen Handling/ use ppez or exp Specimen Handling/mt
 15 or/12-14
 16 11 and 15
 17 ((biliary or bile duct*) adj5 (brush* or scrape)).ti,ab,kf,kw.
 18 16 or 17
 19 animals/ not (humans/ and animals/)
 20 18 not 19
 21 limit 20 to english language
 22 (case reports or comment or editorial or letter).pt.
 23 Case Report/
 24 21 not (22 or 23)
 25 limit 24 to dt=20190530-20211231

 Embase.com (Elsevier)
 # Searches
 1 'bile duct'/exp
 2 'bile duct tumor'/exp
 3 (bile duct* OR biliary OR hilar OR peri?hilar OR klatskin):ti,ab,kw
 4 #1 OR #2 OR #3

5 'stenosis, occlusion and obstruction'/exp
 6 (constriction OR stricture* OR stenosis OR obstruction OR occlusion OR blockage):ti,ab,kw
 7 #5 OR #6
 8 #4 AND #7
 9 'cholestasis'/exp
 10 cholestasis:ti,ab,kw
 11 (('bile duct*' OR biliary OR hilar OR peri?hilar OR klatskin) NEAR/2 (carcinoma* OR adenoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR cholangiocarcinoma* OR malignanc* OR stricture* OR obstruction OR occlusion OR stenosis OR blockage)):ti,ab,kw
 12 #8 OR #9 OR #10 OR #11
 13 Cytodiagnosis/exp
 14 'specimen handling'/exp/mj
 15 'biopsy technique'/exp OR 'biliary tract biopsy'/exp OR 'biopsy brush'/exp
 16 #13 OR #14 OR #15
 17 #12 AND #16
 18 ((biliary OR 'bile duct*') NEAR/5 (brush* OR scrape)):ti,ab,kw
 19 #17 OR #18
 20 animals/exp NOT (humans/exp AND animals/exp)
 21 #19 NOT #20
 22 #21 AND English:la
 23 'case reports':it OR comment:it OR editorial:it OR letter:it OR note:it
 24 'Case Report'/de
 25 #22 NOT (#23 OR #24)
 26 #25 AND [30-05-2019]/sd

Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)] - Wiley ID Search Hits

#1 [mh "Bile Ducts"]
 #2 [mh "Bile Duct Neoplasms"]
 #3 (bile duct* or biliary or hilar or peri?hilar or klatskin):ti,ab
 #4 #1 or #2 or #3

#5 [mh "Constriction, Pathologic"]
 #6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage):ti,ab
 #7 #5 and #6
 #8 #4 and #7
 #9 cholestasis:ti,ab
 #10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) NEAR/2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)):ti,ab
 #11 #8 or #9 or #10
 #12 [mh Cytodiagnosis]
 #13 [mh "Cytological Techniques"]
 #14 [mh "Specimen Handling"]
 #15 #12 or #13 or #14
 #16 #11 and #15
 #17 ((biliary or bile duct*) NEAR/5 (brush* or scrap*)):ti,ab
 #18 #16 or #17
 Date added to CENTRAL trials database: May 30, 2019 - present

Final results after duplicate exclusion and exclusion of studies not fulfilling inclusion criteria: 2

Search strategy for PICO 8:

Search date: Feb 28, 2024

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present; Embase.com (Elsevier) (1947 to 2024 Feb 28; Wiley Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)]

Limits: English, Human

Exclusions: letters, notes, comments, editorials, case reports, reviews

Ovid MEDLINE ALL

1 exp Bile Ducts/ use ppez

2 exp Bile Duct Neoplasms/ use ppez

3 (bile duct* or biliary or hilar or peri?hilar or klatskin).ti,ab,kf,kw.

4 or/1-3

5 exp Constriction, Pathologic/ use ppez

6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage).ti,ab,kf,kw.

7 5 or 6

8 4 and 7

9 exp Cholestasis/ use ppez

10 cholestasis.ti,ab,kf,kw.

11 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage)).ti,ab,kf,kw.

12 or/8-11

13 exp endoscopy, gastrointestinal/ use ppez or exp biliary tract surgical procedures/ use ppez

14 (Choledochoscop* or cholangioscop* or Cholangiopancreatoscop* or spyglass).ti,ab,kf,kw.

15 13 or 14

16 12 and 15

17 animals/ not (humans/ and animals/)

18 16 not 17

19 limit 18 to english language

20 (case reports or comment or editorial or letter).pt.

21 Case Report/

22 19 not (20 or 21)

23 limit 22 to dt=20190530-20211231

Embase.com (Elsevier)

Searches

1 'bile duct'/exp

2 'bile duct tumor'/exp

3 (bile duct* OR biliary OR hilar OR peri?hilar OR klatskin):ti,ab,kw

4 #1 OR #2 OR #3
 5 'stenosis, occlusion and obstruction'/exp
 6 (constriction OR stricture* OR stenosis OR obstruction OR occlusion OR blockage):ti,ab,kw
 7 #5 OR #6
 8 #4 AND #7
 9 cholestasis/exp
 10 cholestasis:ti,ab,kw
 11 (('bile duct*' OR biliary OR hilar OR peri?hilar OR klatskin) NEAR/1 (carcinoma* OR adenoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR cholangiocarcinoma* OR malignanc* OR stricture* OR obstruction OR occlusion OR stenosis OR blockage)):ti,ab,kw
 12 #8 OR #9 OR #10 OR #11
 13 'biliary tract endoscopy'/exp
 14 (choledochoscop* OR cholangioscop* OR cholangiopancreatoscop* OR spyglass):ti,ab,kw
 15 #13 OR #14
 16 #12 AND #15
 17 animals/exp NOT (humans/exp AND animals/exp)
 18 #16 NOT #17
 19 #18 AND English:la
 20 'case reports':it OR comment:it OR editorial:it OR letter:it OR note:it
 21 'Case Report'/de
 22 #19 NOT (#20 OR #21)
 23 #22 AND [30-05-2019]/sd

Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL)] - Wiley
 #1 [mh "Bile Ducts"]
 #2 [mh "Bile Duct Neoplasms"]
 #3 (bile duct* or biliary or hilar or peri?hilar or klatskin)
 #4 #1 or #2 or #3
 #5 [mh "Constriction, Pathologic"]
 #6 (constriction or stricture* or stenosis or obstruction or occlusion or blockage)
 #7 #5 or #6

#8 #4 and #7

#9 cholestasis

#10 ((Bile duct* or biliary or hilar or peri?hilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenosis or blockage))

#11 #8 or #9 or #10

#12 Choledochoscop* or cholangioscop* or Cholangiopancreatoscop* or spyglass

#13 #11 and #12

Date added to CENTRAL trials database: May 30, 2019 - present

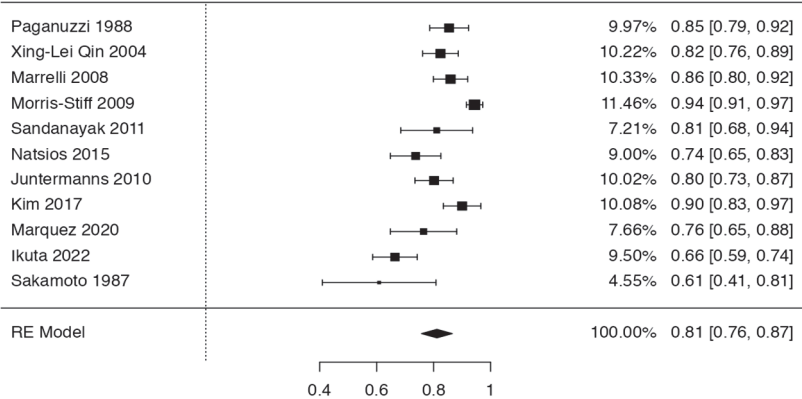
Final results after duplicate exclusion and exclusion of studies not fulfilling inclusion criteria: 13

Table 3s: Studies on CA 19-9 and CEA levels (tumour markers) and their role for differentiating malignant vs benign biliary strictures

Study (year)	Design	Number of patients		Parameters				
		Malignant	Benign	Sensitivity	Specificity	PPV	NPV	Accuracy
CA 19-9 levels								
Sakamoto et al (1987)	Prospective	145	89	-	-	-	-	61%
Paganuzzi et al (1988)	Prospective	49	54	73.9%	87%	-	-	85%
Xing-Lei Qin et al (2004)	Prospective	35	92	77.14%	84.78%	65.85%	90.7%	82.68%
Marrelli et al (2008)	Prospective	87	41	68%	64%	-	-	86%
Morris-Stiff et al (2009)	Prospective	106	142	84.9%	69.7%	67.7%	86.1%	94.56%
Juntermanns et al (2010)	Retrospective	136	0	-	-	-	-	80%
Sandanayak et al (2011)	Prospective	37	48	83%	67%	83%	67%	81.08%
Natios et al (2015)	Prospective	44	51	75%	72.5%	70.2%	77.1%	73.7%
Kim et al (2017)*	Retrospective	80	34	62%*	88%*	-	-	90%
Marquez et al (2020)	Prospective	51	24	-	-	-	-	73.6%
Ikuta et al (2022)	Retrospective	140	0	-	-	-	-	66.4%
CEA levels								
Natios et al (2015)	Prospective	44	51	25%	92.2%	73.3%	58.8%	61%
Budzynska et al (2013)	Prospective	22	18	81.8%	83.3%	85.7%	78.9%	82.5%
Ince et al (2014)	Prospective	129	96	42.7%	89.9%	76%	68%	70%
Lindberg et al (2022)	Prospective	32	25	56%	89%	88%	59%	70%
Abbreviations: PPV positive predictive value; NPV negative predictive value; CEA carcinoembryonic antigen; CA 19-9 carbohydrate antigen 19-9								

Note: Cut-off for CA 19-9 in all studies taken as > 37 U/ml; cut-off of CEA levels taken as $>2-5$ ng/ml;
* This study reports sensitivity and specificity after performing biliary drainage

Figure 1s
a. Pooled accuracy of Ca 19-9 in the discrimination between malignant and benign cause of biliary stricture



b. Pooled accuracy of CEA in the discrimination between malignant and benign cause of biliary stricture

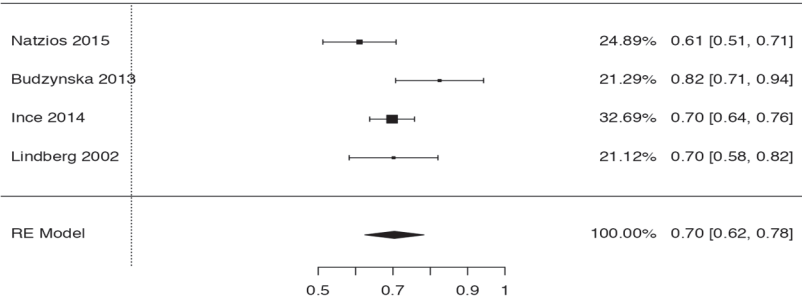


Table 4s: Risk of bias assessment for studies testing CA 19-9 and CEA accuracy for biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Sakamoto 1987	***	NA	**	Good
Paganuzzi 1988	***	NA	**	Good
Xing-Lei Qin 2004	***	NA	**	Good
Marrelli 2008	***	NA	**	Good
Morris-Stiff 2009	***	NA	**	Good
Juntermanns 2010	***	NA	**	Good
Sandanayak 2011	***	NA	**	Good
Natios 2015	***	NA	**	Good
Kim 2017	***	NA	**	Good
Marquez 2020	***	NA	**	Good
Ikuta 2022	***	NA	**	Good
Budzynska 2013	***	NA	**	Good
Ince 2014	***	NA	**	Good
Lindberg 2022	***	NA	**	Good

Table 5s. Table of GRADE evidence

Certainty assessment								Effect estimate	Certainty	Comments
PICO	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
1	11 testing CA 19-9 4 testing CEA	Observational non-randomized	Low	Yes	No	No	No	Pooled accuracy CA 19-9: 81% (76%-87%) Pooled accuracy CEA: 70% (62%-78%)	○○○○○ Very Low	Evidence based on non-randomized observational studies. High inconsistency due to high heterogeneity in the estimates
2	6 assessing the level of the stricture 10 assessing the malignant diagnosis of the stricture	Observational non-randomized	Low	No	No	No	No	Accuracy for detection of the level of the stricture: OR 3.31 (1.20-9.09) Accuracy for the diagnosis of malignancy: OR 2.07 (1.18-3.03)	⊕○○○○ Low	Evidence based on non-randomized observational studies.
3	4	Observational non-randomized	Low	No	No	No	No	Accuracy: EUS-TA+ERCP vs ERCP alone	⊕⊕⊕⊕○ Moderate	Quality of evidence uprated because

								OR 5.77, 3.46-9.63 EUS-TA+ERCP vs EUS-TA alone OR 2.15, 1.23-3.74.		of the great magnitude of the effects (OR>5 vs ERCP alone and OR>2 vs EUS-TA alone)
4	7	Observational non-randomized	Low	Low	Low	High	Low	Same session ERCP+EUS-TA vs ERCP alone: Cannulation rate OR 0.96, 0.32-2.88 Adverse event rate OR 1.22, 0.73-2.03	○○○○○ Very Low	Evidence based on non-randomized studies and further downrating due to high imprecision (wide CIs crossing the unity)
5	10	7 observational studies and 1 meta-analysis	Low	High	Low	Low	Low	The rate of abnormal findings 15.0% , 9%-21% The rate of malignancy <0.1%, 0%-0.1%	○○○○○ Very Low	Based on observational studies, further downrating due to high heterogeneity
6	2	Observational non-randomized studies	Low	Low	Low	Low	Low	Incremental diagnostic yield: 25%, 11%-38%,	⊕○○○○ Low	Based on non-randomized observational studies

								Diagnostic sensitivity: OR 2.72, 1.51-4.87		
7	2	Observational non-randomized studies	Low	Low	Low	Low	Low	Incremental diagnostic yield: 33% (15%-50%)	⊕○○○○ Low	Based on non-randomized observational studies
8	13	12 observational non-randomized and 1 RCT	Low	Low	High	Low	Low	Incremental yield: 27% (10%-45%) Adverse event rate: OR 1.46, 0.84-2.51)	○○○○○ Very Low	Based mainly on non-randomized studies and due to high indirectness for the different standard ERCP modalities used

Table 6s: Studies comparing CECT scan and MRI/MRCP for determining accuracy for the level of obstruction

Study (year)	Design	Total number of cases (n)	CECT scan done in (n)	MRI/MRCP done in (n)	CECT scan (accuracy %)	MRI/MRCP (accuracy %)
Rosch (2002)	Prospective	50	50	50	92%	97%
Upadhyaya (2006)	Prospective	100	28	24	85.71%	95.45%
Jayamohan (2019)	Prospective	33	33	33	88%	100%
Jena (2021)	Prospective	100	100	100	95%	99%
Rao (2014)	Prospective	40	40	40	100%	100%
Singh (2017)	Prospective	57	57	57	100%	100%
Abbreviations: CT computed tomography; MRI magnetic resonance imaging; MRCP magnetic retrograde cholangiopancreatography						

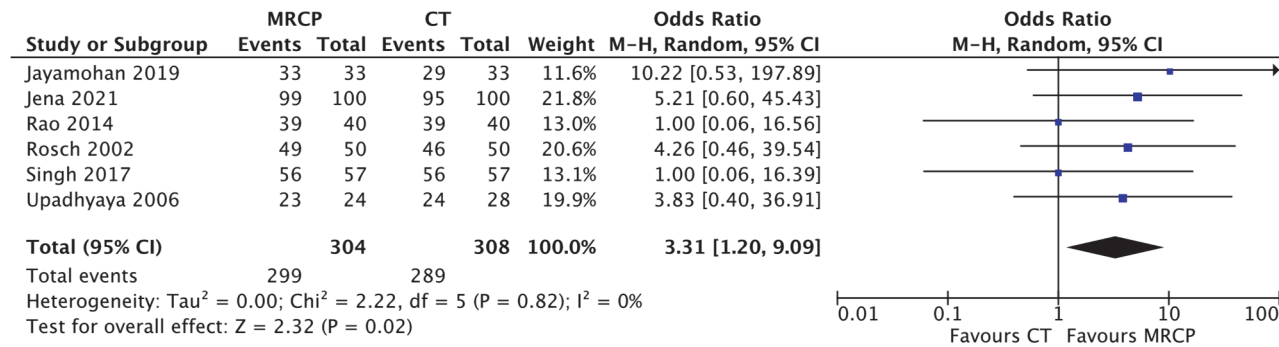
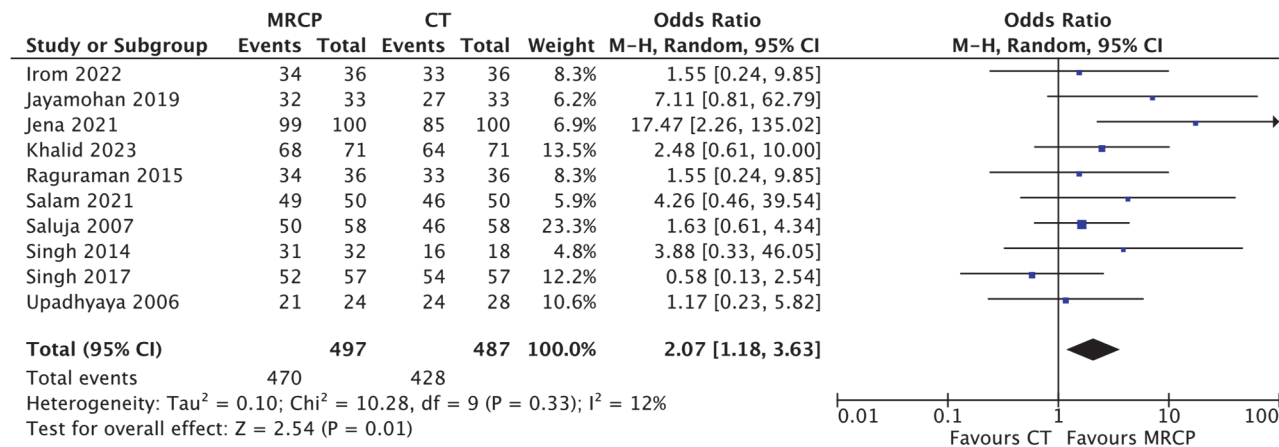
Figure 2s**a. Comparison between MRCP/MRI and CECT-scan in terms of detection of the level of the stricture****b. Comparison between MRCP/MRI and CECT-scan in terms of diagnostic accuracy for malignancy in biliary strictures**

Table 7s: Studies on CECT scan and MRI/MRCP for determining diagnostic accuracy for malignancy in biliary strictures

Study (year)	Design	Total number of cases (n)	CECT scan done in (n)	MRI/MRCP done in (n)	CECT scan (accuracy %)	MRI/MRCP (accuracy %)
Upadhyaya (2006)	Prospective	100	28	24	85.71%	87.5%
Singh (2014)	Prospective	50	18	32	91.43%	98%
Raguraman P (2015)	Prospective	50	36	36	91.6%	94.4%
Jayamohan (2019)_	Prospective	33	33	33	82%	97%
Jena (2021)	Prospective	100	100	100	85%	99%
Salam (2021)	Prospective	50	50	50	91.43%	98%
Irom (2022)	Prospective	36	36	36	91.67%	94.44%
Singh (2017)	Prospective	57	57	57	94.7%	91.22%
Khalid (2023)	Prospective	71	71	71	90.14%	95.77%
Saluja (2007)	Prospective	58	58	58	79.31%	86.2%
Abbreviations: CT computed tomography; MRI magnetic resonance imaging; MRCP magnetic retrograde cholangiopancreatography						

Table 8s: Risk of bias assessment for the studies comparing CECT and MRI/MRCP in the diagnosis of biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Rosch 2002	****	*	***	Good
Upadhyaya 2006	****	*	***	Good
Jayamohan 2019	****	*	***	Good
Jena 2021	****	*	***	Good
Rao 2014	****	*	***	Good
Singh 2017	****	*	***	Good
Raguraman 2015	****	*	***	Good
Salam 2021	****	*	***	Good
Irom 2022	****	*	***	Good
Khalid 2023	****	*	***	Good
Saluja 2007	****	*	***	Good

Table 9s. Summary of studies comparing ERCP-TA with EUS-TA in cases requiring ERCP with biliary drainage for jaundice

Study (Author, year)	Country	Study design	No of patients	Indication	Intervention	Accuracy EUS-TA	Accuracy ERCP-TA	Accuracy EUS-TA + ERCP-TA
Weilert, 2014	USA	Prospective, single center	15	Suspected malignant biliary obstruction (both benign + malignant)	EUS-FNA for tissue sampling prior to ERCP-TA same session	12/15 (80%)	12/15 (80%)	NA
Moura, 2018	Brasil	Prospective, single center	50	Suspected malignant biliary stricture	EUS+ERCP-TA vs EUS-TA vs ERCP-TA	47/50 (94%)	31/50 (62%)	49/50 (98%)
Jo, 2019	Korea	Retrospective, multicenter	84	Suspected malignant biliary obstruction	EUS+ERCP-TA vs. EUS-FNA vs. ERCP-TA	64/84 (76%)	63/84 (75%)	78/84 (93%)
Yeo, 2019	Korea	Retrospective, single center	41	Biliary obstruction (different tumor sites)	ERCP-TA vs. EUS-FNA	36/41 (88%)	33/41 (80%)	NA
Onoyama, 2019	Japan	Retrospective, single center	73	Extrahepatic colangiocarcinomas	EUS-FNA vs. ERCP biliary biopsy	16/19 (84%)	48/54 (89%)	NA
Chung, 2021	Korea	Retrospective, single center	85	Suspected biliary stricture	ERCP-TA vs. EUS-TA	71/85 (84%)	62/85 (73%)	NA
Sobhrakhshankhak, 2021	Iran	Prospective, single center	60	Suspected malignant biliary stricture	EUS-FNA vs. ERCP brushings	48/60 (80%)	33/60 (55%)	52/60 (87%)
Mathew, 2022	India	Retrospective, single center	77	Malignant biliary obstruction	EUS-FNA vs ERCP brushings	71/77 (92%)	55/77 (71%)	NA

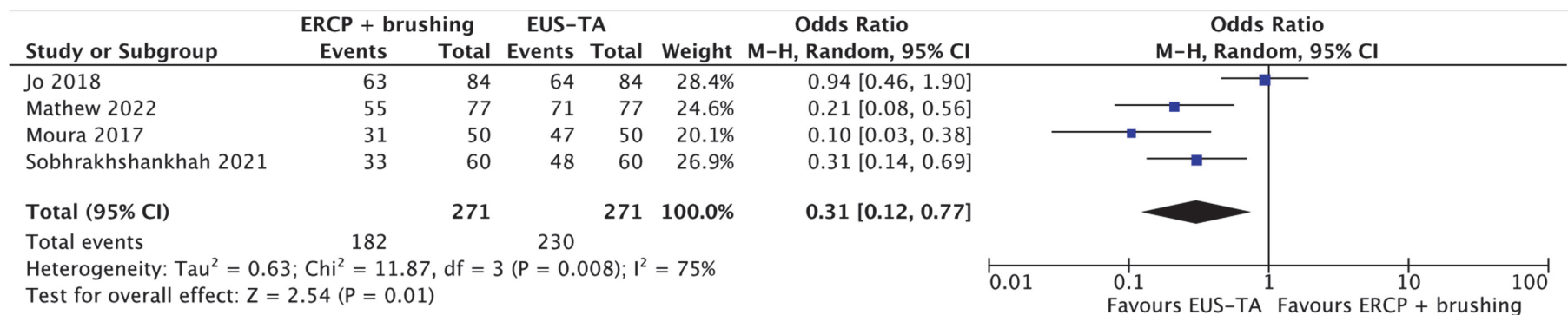
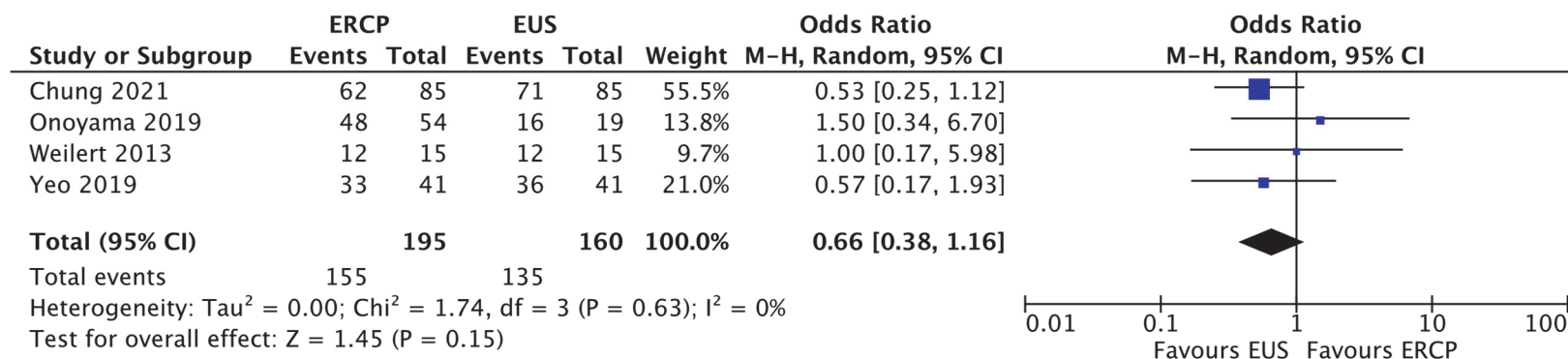
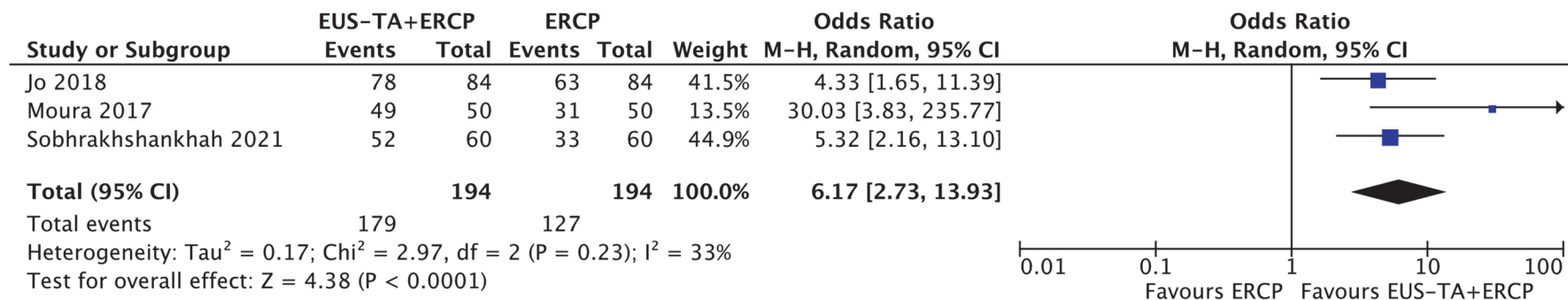
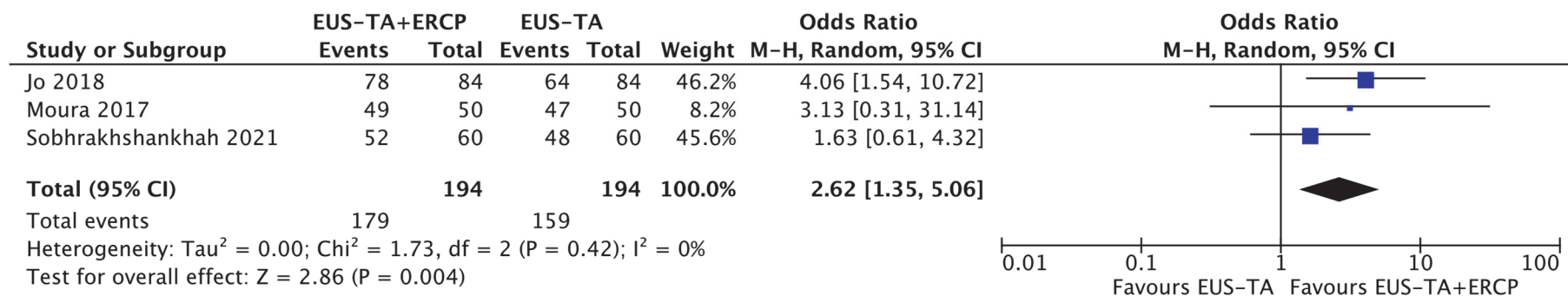
Figure 3s**a. Comparison in terms of accuracy between ERCP + brushing vs EUS-TA for distal biliary strictures****b. Comparison in terms of accuracy between ERCP+ biopsies vs EUS-TA for distal biliary strictures**

Figure 4s**a. Comparison in terms of accuracy between EUS-TA+ERCP vs ERCP alone for distal biliary strictures****b. Comparison in terms of accuracy between EUS-TA+ERCP vs EUS-TA alone for distal biliary strictures**

c. Incremental diagnostic yield for diagnosing malignancy of EUS-TA+ERCP vs ERCP alone for distal biliary strictures

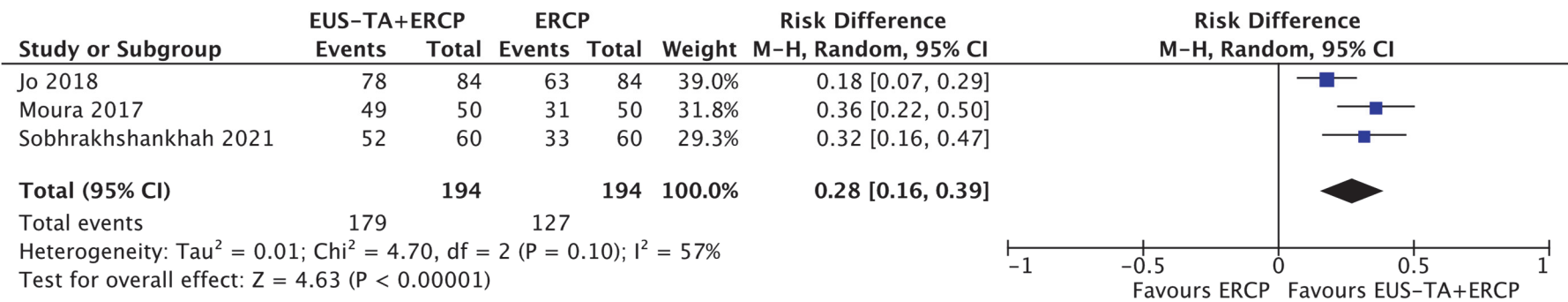


Table 10s: Risk of bias assessment of the studies comparing different sampling modalities for distal biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Ross, 2008	****	*	**	Good
Weilert, 2014	****	*	**	Good
Moura, 2018	****	*	***	Good
Jo, 2019	****	*	***	Good
Yeo, 2019	****	*	**	Good
Onoyama, 2019	****	*	**	Good
Chung, 2021	****	*	**	Good
Sobhrakhshankhak, 2021	****	*	***	Good
Mathew, 2022	****	*	**	Good

Table 11s: Baseline characteristics of the studies comparing same session ERCP+EUS-TA vs ERCP alone

Study (Author, year)	Country	Study design	No of patients	Male sex (%)	Adverse events rate	Bile duct cannulation rate
Gorris, 2021	Netherlands	Retrospective, 2 centers	Same session: 118 Separate session: 51	52%	Same session: 43/118 (36%) Separate session: 10/51 (20%)	NA
Purnak, 2021	USA	Retrospective, single center	Same session: 88 Separate session: 37	47%	Same session: 2/88 (2%) Separate session: 3/37 (8%)	Same session: 87/88 (99%) Separate session: 35/37 (95%)
Chu, 2013	China	RCT, single center	Same session: 60 Separate session: 60	53%	Same session: 10/60 (17%) Separate session: 8/60 (13%)	Same session: 59/60 (98%) Separate session: 59/60 (98%)
Camus, 2012	France	Retrospective, single center	Same session: 122 ERCP alone: 68	57%	Same session: 22/122 (18%) Separate session: 11/68 (16%)	Same session: 119/122 (98%) Separate session: 66/68 (97%)
Aslanian, 2011	USA	Retrospective, single center	Same session: 29 Separate session: 18	60%	Same session: 1/29 (3%) Separate session: 0/18 (0%)	Same session: 21/29 (72%) Separate session: 16/18 (88%)
Vila, 2011	Spain	Retrospective, single center	Same session: 39 Separate session: 46	NA	Same session: 5/39 (13%) Separate session: 8/46 (17%)	NA

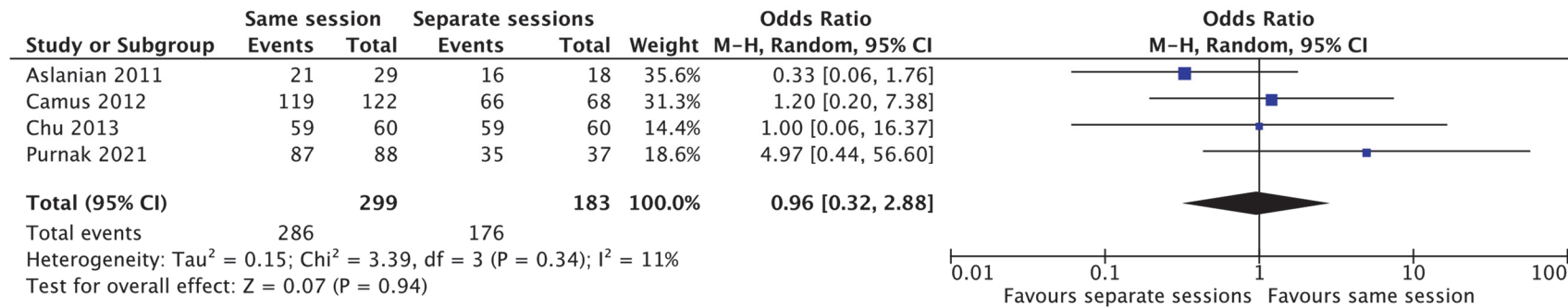
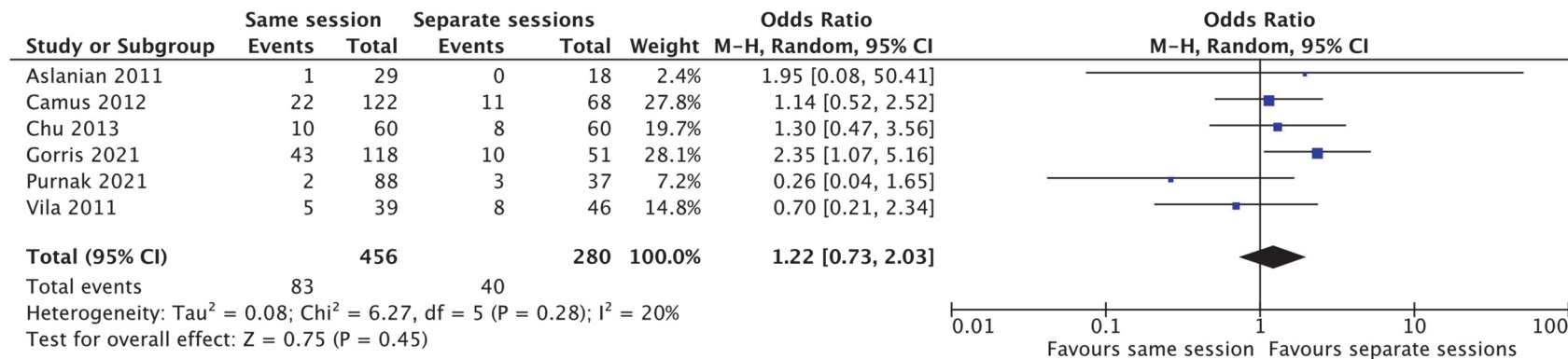
Figure 5s**a. Comparison of cannulation rate between combined ERCP+EUS-TA vs ERCP alone****b. Comparison of adverse event rate between combined ERCP+EUS-TA vs ERCP alone**

Table 12s: Risk of bias assessment of the studies comparing same session ERCP+EUS-TA vs ERCP alone

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Aslanian, 2011	****	*	***	Good
Camus, 2012	****	*	***	Good
Chu, 2013	****	*	**	Good
Gorris, 2021	****	*	**	Good
Purnak, 2021	****	*	**	Good
Vila, 2011	****	*	**	Good

Table 13s: Studies assessing the role of EUS in patients with dilated CBD and normal liver function tests

Study (Author, year)	Country	Study design, centers	No. of patients	Male sex (%)	Abnormal findings	Malignancy
Chhoda, 2021	USA	Metanalysis	1262	20-40%	9.4%	0.5%
Rana, 2013	India	Retrospective, single center	30	63%	10/30 (33.3%)	0%
Attila, 2011	USA	Retrospective, single center	20	NA	7/20 (35%)	0%
Bruno, 2014	Italy	Retrospective, single center	57	25%	12/57 (21%)	3/57 (5.2%)
Kaspy, 2019	Canada	Retrospective, single center	199	19.5%	19/199 (9.5%)	0%
Sousa, 2019	Portugal	Retrospective, single center	21	60.3%	4/21 (19%)	0%
Malik, 2007	USA	Retrospective, single center	32	9%	2/32 (6.2%)	0%
Oppong, 2014	UK	Retrospective, single center	40	27%	5/40 (12.5%)	0%

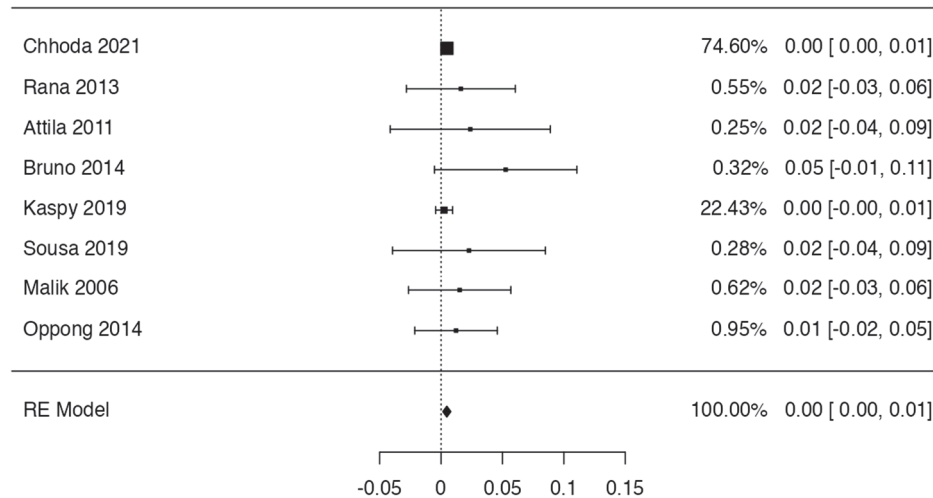
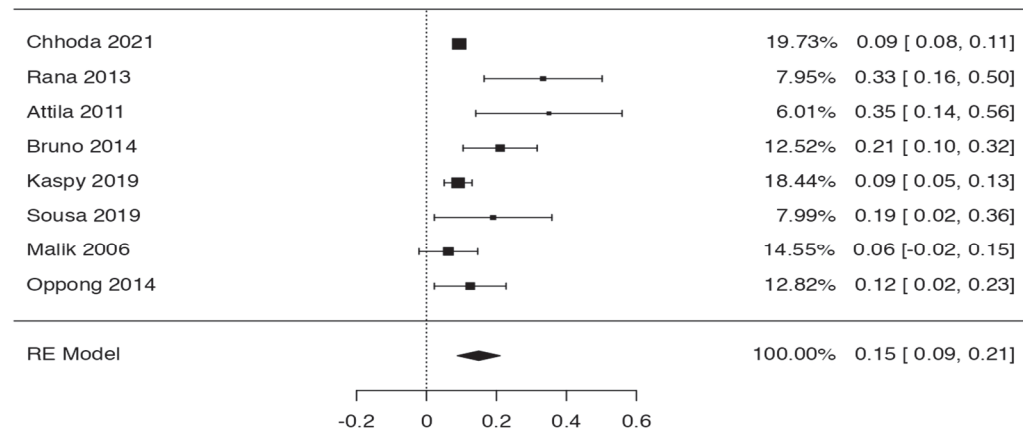
Figure 6s**a. Pooled malignancy rate of EUS in patients with CBD dilation and normal liver function tests****b. Pooled rate of abnormal findings with EUS in patients with CBD dilation and normal liver function tests**

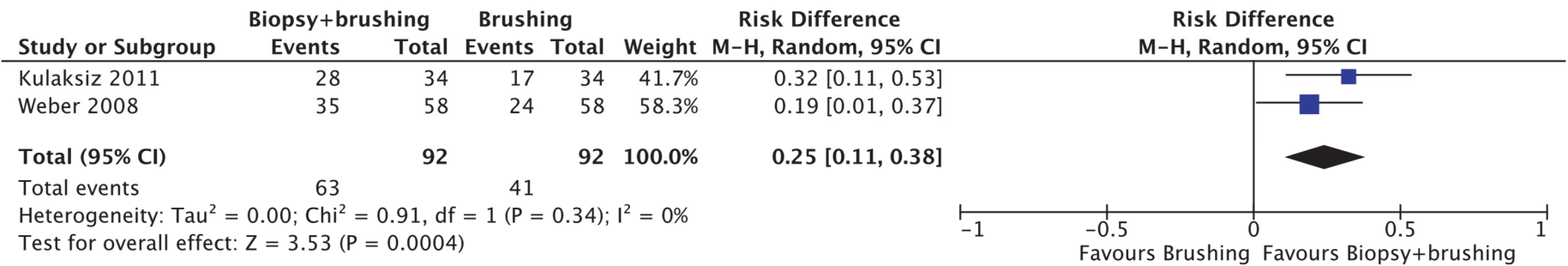
Table 14s: Risk of bias assessment for the studies assessing the role of EUS in patients with CBD dilation and normal liver function tests

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Chhoda, 2021	****	NA	**	Good
Attila, 2011	***	NA	**	Good
Bruno, 2014	***	NA	**	Good
Kaspy, 2019	***	NA	**	Good
Malik, 2007	***	NA	**	Good
Oppong, 2014	***	NA	**	Good
Rana, 2013	***	NA	**	Good
Sousa, 2019	***	NA	**	Good

Table 15s: Studies comparing ERCP with biopsy+brushing vs ERCP with brushing alone in patients with perihilar biliary strictures

Author (year)	Design	N	Intervention	Population	Sensitivity	Specificity
Weber, 2008	Retrospective	58	Biopsy vs brushing vs biopsy + brushing (B+B)	Patients with hilar cholangiocarcinoma	Brush: 41.4% Biopsy: 53.4% B+B: 60.3%	Not described
Kulaksiz, 2011	Prospective	43	Biopsy vs brushing vs biopsy + brushing (B+B)	Patients with suspected malignant proximal biliary stricture	Brush: 49% Biopsy: 69% B+B: 80%	Brush: 100% Biopsy: 100%

Figure 7s
a. Incremental diagnostic yield for malignancy of ERCP with biopsy+brushing as compared to ERCP with brushing alone for perihilar biliary strictures.



b. Diagnostic sensitivity for malignancy of ERCP with biopsy+brushing as compared to ERCP with brushing alone for perihilar biliary strictures.

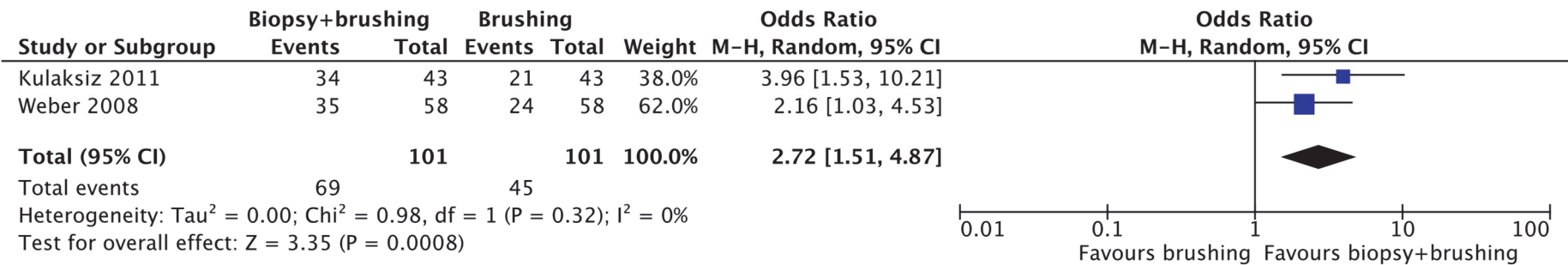


Table 16s: Studies comparing ERCP with biopsy+brushing vs ERCP with brushing alone in patients with perihilar biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Weber, 2008	**	**	***	Moderate
Kulaskiz, 2011	**	**	**	Moderate

Table 17s: Studies assessing the role of EUS-tissue acquisition in patients with peri-hilar biliary strictures

Study	Nr of perihilar strictures/patients	Sensitivity	Specificity	NPV	PPV	Diagnostic accuracy	AEs
DeWitt, 2006	24	77%	100%	29%	NR	79%	0%
Fritscher-Ravens, 2000	10	89%	NR	NR	NR	89%	0%
Fritscher-Ravens, 2004	44	89%	100%	NR	NR	91%	0%
Mohamadnejad, 2011	30	59%	NR	NR	NR	NR	1.4%
Mohkam, 2017	102	69%	100%	58%	100%	78%	NR
*Moura, 2018	15	86.7%	NR	NR	100%	86.7%	0%
Ohshima, 2011	9	100%	100%	100%	100%	100%	0%
Raine, 2020	45	86%	NR	40%	NR	NR	NR
*Sobhrakhshankhah, 2021	32	73.3%	100%	100%	NR	NR	0%
Nayar, 2011	32	52%	100%	54%	100%	68%	NR
NPV: negative prognostic value; PPV: positive prognostic value; AE: adverse events							
*Comparative study (EUS-FNB vs. ERCP brushing)							

Figure 8s. Incremental yield for diagnosis malignancy of EUS-TA + ERCP vs ERCP-biopsies/brushing alone in patients with peri-hilar biliary strictures.

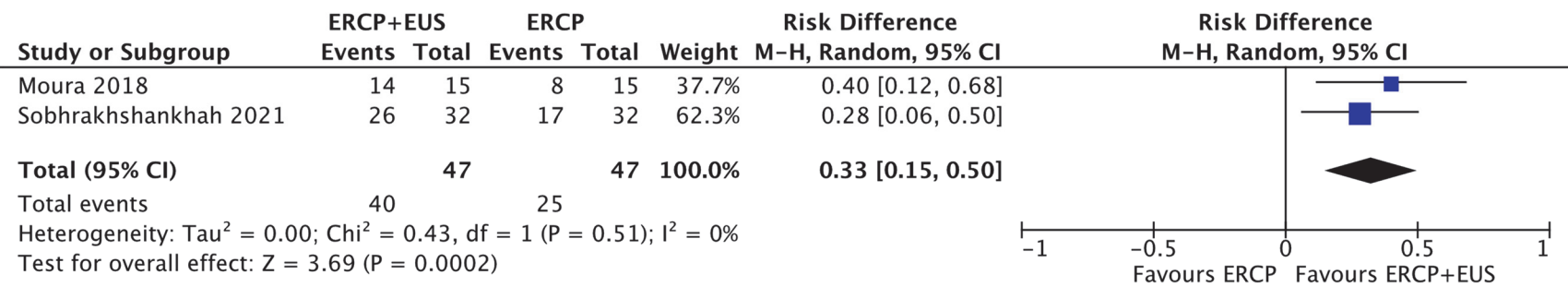


Table 18s: Studies comparing ERCP with biopsy vs EUS-TA in patients with perihilar biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Moura, 2018	***	**	***	High
Sobhrakhshankha, 2021	***	**	***	High

Table 19s. Cholangioscopy approaches: Technique, pro and cons.

Single operator cholangioscopy (SOC): Single-operator cholangioscopy (SOC) enables a single endoscopist to perform cholangioscopy using the “mother-baby” method, wherein a slim, disposable endoscope passes through the working channel of a duodenoscope. SOC boasts a high reported success rate, providing stable positioning and adequate access to the intra-hepatic tree. The drawbacks of SOC include the significant cost associated with the dedicated processor and disposable components, as well as the absence of virtual chromoendoscopy. However, image quality has improved over the last few years, and AI-based systems have been specifically trained with SOC images, potentially allowing for a future role in assisting the endoscopist in optical diagnosis and/or targeting biopsies.
Dual operator “mother-baby” cholangioscopy (DOC): The traditional dual-operator cholangioscopy (DOC), where a second endoscopist inserts and manipulates an extremely thin reusable endoscope through the working channel of a duodenoscope, has largely been supplanted by SOC. This shift is primarily attributed to the cost and fragility of the equipment, leading to a limited body of literature endorsing its application.
Direct cholangioscopy (DC): Direct cholangioscopy (DC) involves utilizing non-specific endoscopes to directly access the common bile duct. Slim or ultraslim endoscopes, intended for pediatric or transnasal esophagogastroduodenoscopy, are typically preferred. High-definition imaging and virtual chromoendoscopy can theoretically assist in distinguishing neoplastic from non-neoplastic strictures, however, definitive visual criteria for malignancy have not been developed. Furthermore, even if using different strategies (i.e. balloon-assisted, tandem technique), the biliary access is technically challenging, with reported high level of variability in term of success rate, and difficult access to intra-hepatic ducts. Moreover, the safety of direct cholangioscopy is in doubt due to the adjunctive burden of rare yet severe adverse events (i.e. stroke resulting from air leakage into the portal or hepatic venous system).

Table 20s: Studies comparing standard ERCP modalities vs ERCP with cholangioscopy in patients with biliary strictures

Reference	Study design	Patients, n	Sensitivity	Specificity	Accuracy	Adverse Events
Gerges 2020	Multicenter RCT	Brushing: 27 SOC: 30	Brushing: 21.4% SOC: 68.2%	Brushing: 84.6% SOC: 62.5%	Brushing: 51.9% SOC: 66.7%	Brushing: 1 cholangitis, 1 cholecystitis, 1 bleeding. SOC: 2 pancreatitis
Sekine 2022	Multi-center retrospective study	59	Biopsies: 64.0% SOC: 54.0%	Biopsies: 100.0% SOC: 100.0%	Biopsies: 69.5% SOC: 61.0%	5 cholangitis
Draganov 2012	Single-center prospective study	26	Brushing: 5.9% Biopsies: 29.4% SOC: 76.5%	Brushing: 100.0% Biopsies: 100.0% SOC: 100.0%	Brushing: 38.5% Biopsies: 53.8% SOC: 84.6%	\
Fukuda 2005	Single-center retrospective study	97	ERC-tissue sampling: 57.9% ERC-tissue sampling + SOC: 100%	ERC-tissue sampling: 100% ERC-tissue sampling + SOC: 86.8%	ERC-tissue sampling: 78.1% ERC-tissue sampling + SOC: 93.4%	\
Han 2020	Single-center retrospective study	619	Brushing (n = 614): 38.5% Biopsies (n = 259): 50.0% SOC/DOC (n = 83): 51.1%	Brushing (n = 614): 99.3% Biopsies (n = 259): 96.7% SOC/DOC (n = 83): 67.30%	\	\
Hartman 2012	Single-center retrospective study	110	Biopsies: 76.0% SOC: 57.0%	Biopsies: 100.0% SOC: 100.0%	Biopsies: 88.0% SOC: 78.0%	\
Lee 2019	Single-center prospective study	32	SOC: 92.3%	SOC: 100%	SOC: 93.6%	\
Onoyama 2020	Single-center retrospective study (propensity score matched)	62	Biopsies: 82.4% SOC: 83.3%	Biopsies: 100.0% SOC: 100.0%	Biopsies: 90.3% SOC: 90.3%	Biopsies: 9 pancreatitis, 3 cholangitis SOC: 6 pancreatitis, 2 cholangitis, 1 bleeding
Walter 2016	Single-center retrospective study	Biopsies: 68 DC: 38	Biopsies: 45.7% DC: 58.3%	Biopsies: 100.0% DC: 100.0%	\	\

Yan 2019	Single-center retrospective study	50	Biopsies: 37.5% SOC: 60.0%	Biopsies: 100.0% SOC: 100.0%	\	1 bleeding, 1 cholangitis
Kato 2019	Single-center retrospective study	Brushing: 14 SOC: 20	Brushing: 87.5% SOC: 90.0%	Brushing: 83.3% SOC: 90.0%	Brushing: 85.7% SOC: 90.0%	Brushing: 3 pancreatitis, 2 cholangitis SOC: 3 pancreatitis, 1 bleeding, 1 cholangitis
Tischendorf 2005	Single-center prospective study	53	ERC-tissue sampling: 66.0% SOC: 92.0%	ERC-tissue sampling: 51.0% SOC: 93.0%	ERC-tissue sampling: 55.0% SOC: 93.0%	\

Figure 9s: Incremental yield of ERCP with cholangioscopy compared to standard ERCP

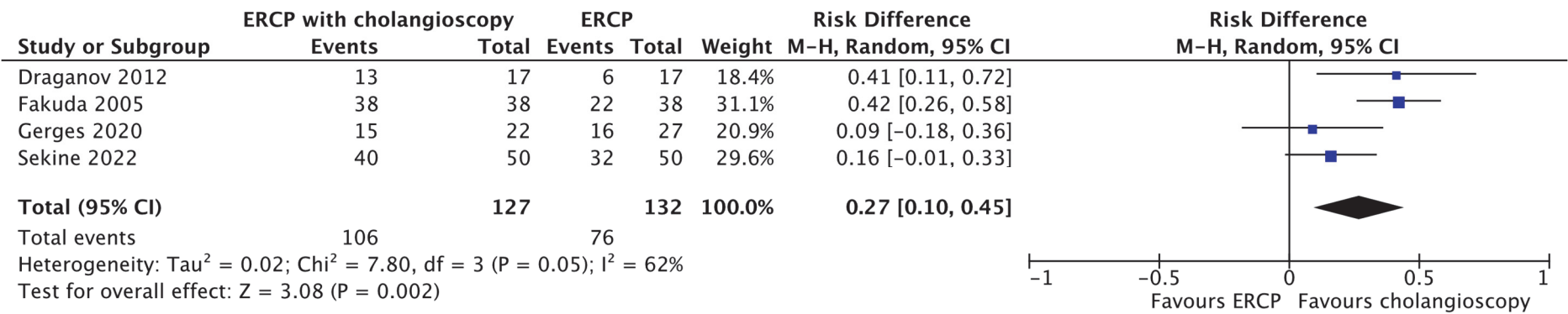


Figure 10s: Sensitivity of ERCP with cholangioscopy as compared to standard ERCP

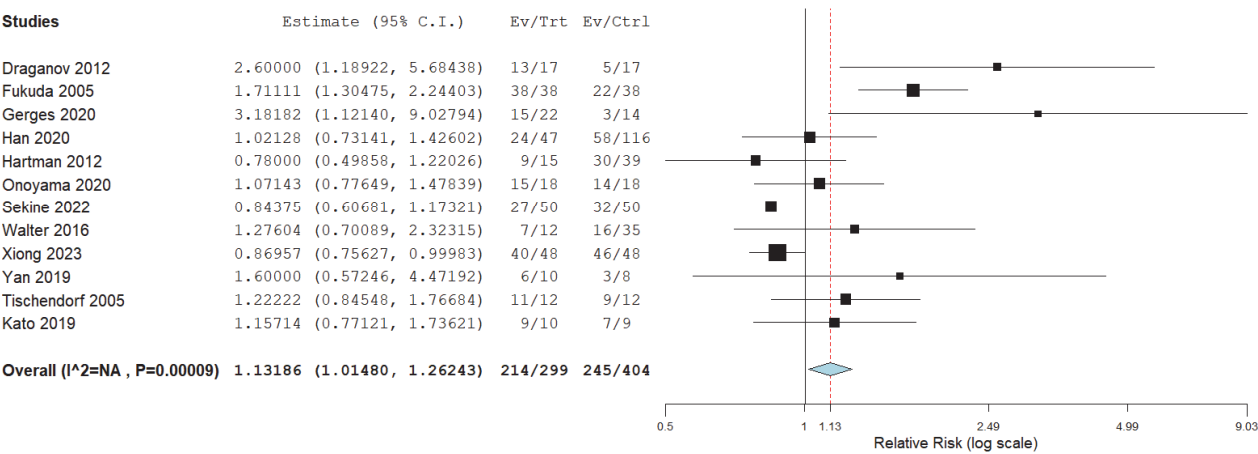


Figure 11s: Comparison of adverse event rate between ERCP with cholangioscopy vs standard ERCP

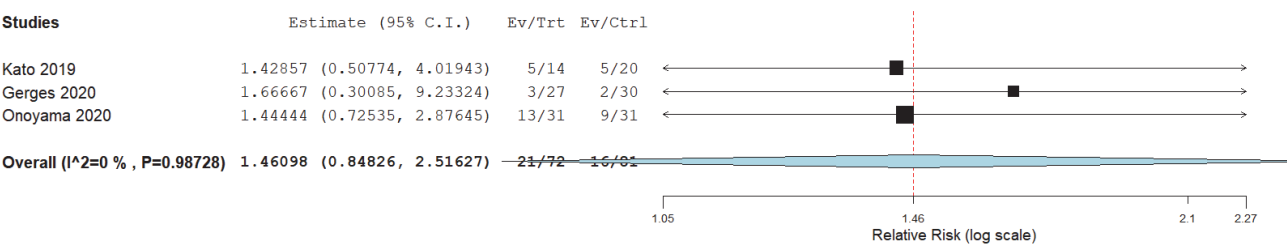


Table 21s: Risk of bias assessment of the studies comparing ERCP with cholangioscopy vs standard ERCP in patients with biliary strictures

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcomes (max 3 stars)	Quality
Gerges 2020	*****	**	**	Good
Sekine 2022	***	**	**	Good
Draganov 2012	***	**	**	Good
Fukuda 2005	***	**	**	Good
Han 2020	***	**	**	Good
Hartman 2012	***	**	**	Good
Lee 2019	***	**	**	Good
Onoyama 2020	***	**	**	Good
Walter 2016	***	**	**	Good
Yan 2019	***	**	**	Good
Kato 2019	***	**	**	Good
Tischendorf 2005	***	**	**	Good